South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 9, 2023

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

June 9, 2023
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_MjJhYTE3YmYtOGVlNy00MzlkLTkyM2EtMjA3ZDA5NThkOWRl%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
425899727@t.plcm.vc
Video Conference ID: 119 968 909 64

Join by phone
+1 952-222-7450
Phone Conference ID: 593 250 179#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Eucrisa review**
- **Vtama PA**
- **Winlevi PA**
- **Opioid update**

New business
- **Antidepressant PA review**
- **Asthma guidelines**
- **Sotyktu**

Public input accepted after individual topic discussion
Next meeting date September 8, 2023 & adjournment

South Dakota Department of Social Services, Division of Medicaid Services
Pharmacy & Therapeutics (P&T) Committee Meeting Minutes

Friday, March 24, 2023
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Heather Preuss, MD	
Dana Darger, RPh, Chair	X	Matthew Stanley, DO	
Mikel Holland, MD		Deidre Van Gilder, PharmD	X
Bill Ladwig, RPh	X	Mike Jockheck, DSS Staff	X
Kelley Oehlke, PharmD	X	Matthew Ballard, DSS Staff	
Lenny Petrik, PharmD		Sarah Aker, DSS Staff	

Administrative Business

Darger called the meeting to order at 1:03 pm. The minutes of the December meeting were presented. Ladwig made a motion to approve. Baack seconded the motion. The motion was unanimously approved.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from October 1, 2022, to December 31, 2022. A total of 1,968 PAs were reviewed of which 100 requests (5.1%) were received via telephone and 1,297 requests (65.9%) were received via fax, and 571 (29%) were reviewed via electronically. There was a 6.3% increase of PAs received compared to the previous quarter. Under the Top 5 therapeutic classes for PAs, Baack inquired on the sertraline PAs listed next to the Antidepressants. An in-depth review was requested.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from October 1, 2022, to December 31, 2022. The top five therapeutic classes based on paid amount were atypical antipsychotics, skin and mucous membrane agents, disease-modifying anti-rheumatic agents, hemostatics, and amphetamines. These top 15 therapeutic classes comprise 25.82 % of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 9.23% of total claims. There was a notable increase in antibiotic prescriptions which corresponded with the 2022-2023 flu season peaking early. Baack commented on seeing more patients using Xolair at her practice. Of interest, Darger commented on the new biosimilar approved in January.

Darger inquired if there was any public testimony. There were none.

Old Business

Fleqsuvy & baclofen review

The committee reviewed Fleqsuvy and baclofen utilization. Fleqsuvy was reviewed at the June P&T meeting the previous year. Committee had requested to review Fleqsuvy utilization when utilization increased. Darger commented that Fleqsuvy suspension is in a concentrated form compared to the solution. Baack said the liquid form is convenient for older children with a g-tube. After further discussion, committee requested to review Fleqsuvy and baclofen next year with a breakdown in quantity and cost per dose.

Selgentis & tramadol review
The committee reviewed Selgentis and tramadol utilization. Seglentis was reviewed at the September P&T meeting the previous year. After discussion, committee was satisfied with the utilization and only asked to bring it back if utilization increased significantly.

Vuity & pilocarpine review
The committee reviewed Vuity and pilocarpine utilization. Vuity was reviewed at the March P&T meeting the previous year. After reviewing utilization over three quarters, Ladwig commented his surprise that Vuity didn't take off as expected but expressed the need for continual monitoring and to review next year.

Darger inquired if there was any public testimony. There were none.

Opioid update
The committee reviewed 4Q2022 opioid outcomes compared to previous quarters from the opioid initiatives. There was a decrease in opioid utilization and utilizers during 4Q2022 even with an increase in total eligibility and utilizers. Darger inquired if there was any public testimony. There was none. Darger commented the initiatives that are continuing to work. Ladwig concurred.

New Business

Dermatological PA review
Baack expressed the need to review the Dermatological PAs at the last meeting concentrating on diagnosis of atopic dermatitis, psoriasis, rosacea, and topical acne treatments. The committee reviewed the Opzelura PA reviews and utilization which compared the first half of 2022 to second half of 2022. Baack questioned if Eucrisa should be on PA. An in-depth review of Eucrisa utilization including age breakdown, diagnosis of atopic dermatitis, length of therapy, taxonomy of prescribers, and other state PA criteria on Eucrisa were requested.

The committee reviewed other drugs used for psoriasis and atopic dermatitis. After discussion, Baack motioned to add PA to Vtama to indication. Ladwig seconded the motion. Darger inquired if there was any public testimony. There was none. The motion was approved unanimously.

The committee reviewed rosacea and topical acne PA reviews and utilization. After discussion, Baack motioned to remove generics such as adapalene/Differin cream, adapalene /Differin gel, adapalene-benzoyl gel, benzoyl-erythromycin gel, clindamycin-benzoyl peroxide gel, tretinoin microsphere gel/pump, tazarotene cream from the topical acne PA. Oehlke seconded the motion. Darger inquired if there was any public testimony. There was none. The motion was approved unanimously.

The committee reviewed the rosacea PA reviews and utilization. After discussion, Baack motioned to remove metronidazole gel 1% from the rosacea PA criteria and add Winlevi cream to it. Ladwig seconded the motion. Darger inquired if there was any public testimony. There was none. The motion was approved unanimously.

Mupirocin trend
The committee reviewed an in-depth analysis of mupirocin utilization at Darger's request since it had climbed to the top 50 drug based on number of claims. Most of the utilization was concentrated at the two years age span. Baack commented on its use for impetigo. The committee was satisfied with the review.

Epinephrine trend
The committee reviewed an in-depth review of epinephrine utilization since it had climbed the top 50 drugs by paid amount. AUVI-Q-Q utilization was noted during January 2023. Both Van Gilder and Oehlke provided information that AUVI-Q is a guided epinephrine injection that provides audio and visual ques that may be useful especially for children. Darger and Ladwig commented on adding AUVI-Q to PA. After discussion, it was requested to bring AUVI-Q back to the next meeting; providing utilization and break down on age including other state's PA criteria.

Darger inquired if there was any public testimony. There was none.

Review PA forms & criteria
The committee reviewed the PA forms and criteria. Jockheck provided an update on the Hepatitis C PA criteria. Effective April 1, 2023, the sobriety requirement, metavir score, fibroscan score, APRI score, and documentation of severe manifestations of hepatitis C will be removed.

Jockheck also mentioned the drug Makena will be removed from the market. Darger commented lindane and Sklice are no longer available on the market. Baack said there are new asthma guidelines and the need to review asthma drugs as a class. She will invite a pulmonologist to the June meeting. Ladwig commented on the GLP-1 PA criteria. The committee discussed what qualifies for type 2 diabetes. Ladwig said Brisdelle is no longer available as brand. Jockheck said next time the PA forms and criteria are reviewed, the number of requests for each PA will also be provided.

Baack motioned to accept the PAs with few changes discussed. Ladwig seconded the motion. Darger inquired if there was any public testimony. There were none. The motion was approved unanimously.

Xelstrym
Xelstrym clinical information was presented for review. After discussion, committee requested to review if utilization increased in volume. Darger inquired if there was any public testimony. There were none.

Jockheck provided an update from Sam Moon from the Department of Medical Services on follow up care for children prescribed ADHD medications and metabolic monitoring for children and adolescents on antipsychotics. The review at previous meetings had seem to show that patients were not receiving metabolic check-ups, but many are receiving it. However, there is still room for improvement, but not as bad as initially thought.

Darger announced his retirement from the P&T Committee after serving 18 years. December will be his last meeting. Van Gilder accepted the role of chairman starting in 2024.

Adjournment
The next meeting scheduled on June 9, 2023. The September meeting is tentatively scheduled for September 8, 2023. The December meeting is tentatively scheduled for December 8, 2023. Ladwig made a motion to adjourn the meeting and Baack seconded the motion. The motion passed unanimously, and the meeting adjourned at 2:52 pm CT.

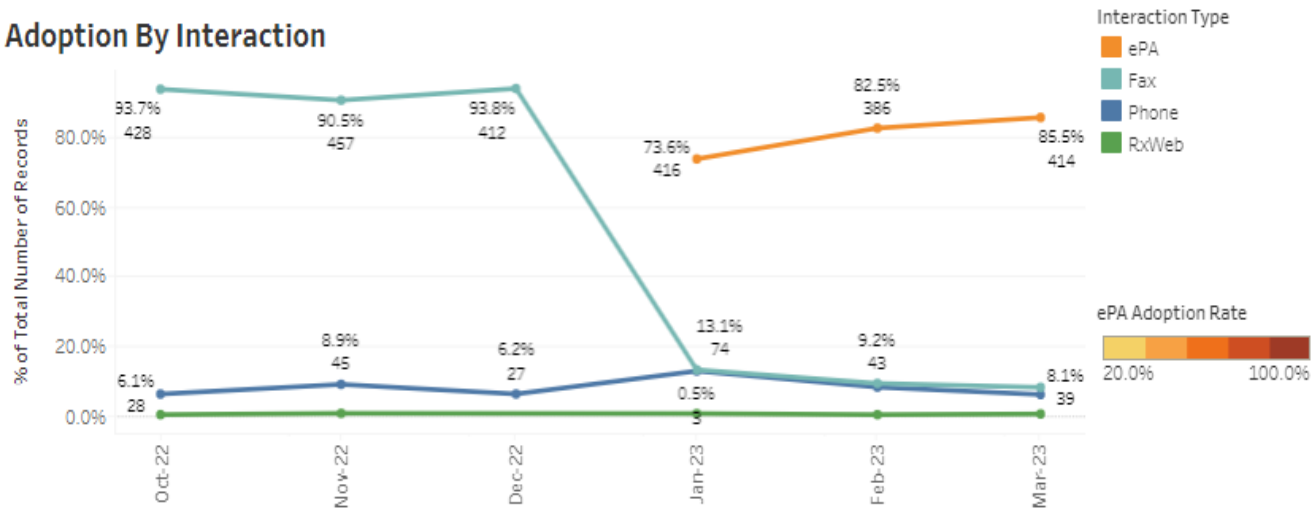
PA Report
1/1/2023 – 3/31/2023

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	2,222	2,222	0	100.00%	0.00%
Urgent	237	237	0	100.00%	0.00%
Grand Total	**2,459**	**2,459**	**0**		

Priority	Standard	Urgent
ePA	1,009	207
Fax	149	7
Phone	124	23
Real-Time	940	

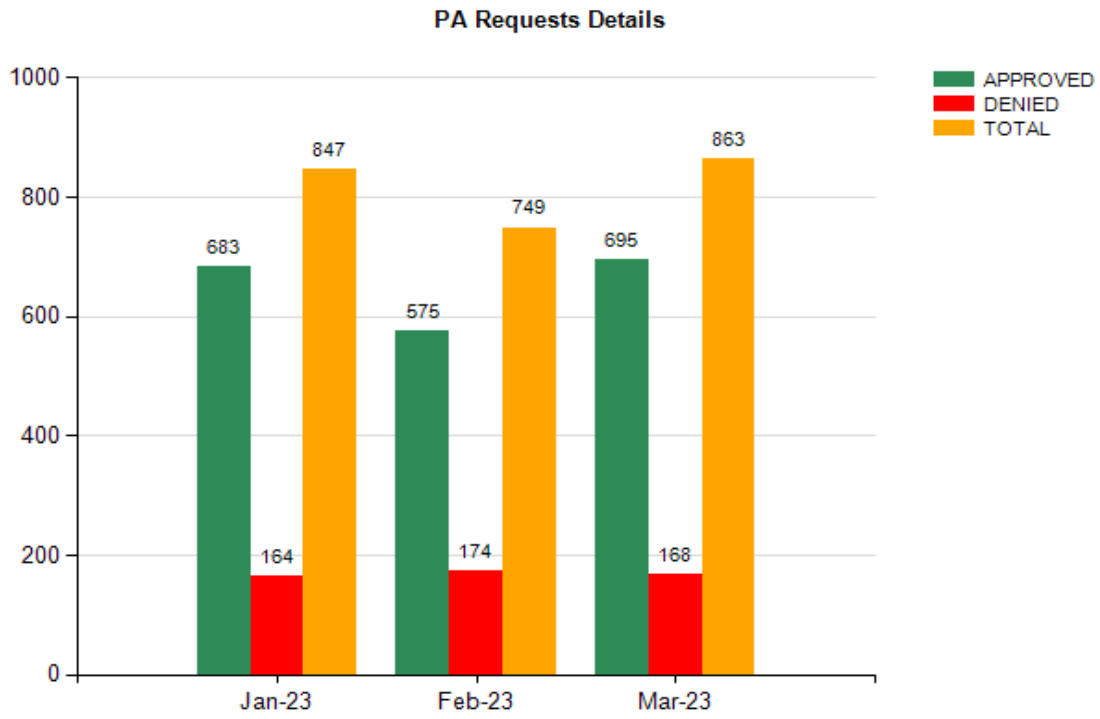
Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**2,459**	**147**	**6%**	**156**	**6.3%**	**940**	**38.2%**	**1,216**	**49.5%**



This graph shows the adoption of Interaction Types in percentage. This graph considers all resolved cases (Approved + Denied).

PA Initial Requests Summary

Month	Approved	Denied	Total
Jan-23	683	164	847
Feb-22	575	174	749
Mar-23	695	168	863
1Q2023	**1,953**	**506**	**2,459**
Percent of Total	**79.42%**	**20.58%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIPSYCHOTICS/ANTIMANIC	493	22	515	95.73%	20.94%	, VRAYLAR
ANTIDIABETICS	328	92	420	78.10%	17.08%	, OZEMPIC
ANALGESICS - OPIOID	148	46	194	76.29%	7.89%	HYDROCODONE/APAP, TRAMADOL
ANTIDEPRESSANTS	171	19	190	90.00%	7.73%	, SERTRALINE HCL
DERMATOLOGICALS	106	68	174	60.92%	7.08%	DUPIXENT,
OTHERS -	707	259	966	73.19%	39.28%	
1Q23	**1,953**	**506**	**2,459**	**79.42%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	493	22	515	95.73%
27 - ANTIDIABETICS*	328	92	420	78.10%
65 - ANALGESICS - OPIOID*	148	46	194	76.29%
58 - ANTIDEPRESSANTS*	171	19	190	90.00%
90 - DERMATOLOGICALS*	106	68	174	60.92%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	108	48	156	69.23%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	120	18	138	86.96%
67 - MIGRAINE PRODUCTS*	85	46	131	64.89%
52 - GASTROINTESTINAL AGENTS - MISC.*	76	25	101	75.25%
66 - ANALGESICS - ANTI-INFLAMMATORY*	55	15	70	78.57%
16 - ANTI-INFECTIVE AGENTS - MISC.*	43	2	45	95.56%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	18	23	41	43.90%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	28	4	32	87.50%
72 - ANTICONVULSANTS*	26	3	29	89.66%
12 - ANTIVIRALS*	7	21	28	25.00%
41 - ANTIHISTAMINES*	19	6	25	76.00%
83 - ANTICOAGULANTS*	19	4	23	82.61%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	19	1	20	95.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	15	3	18	83.33%
54 - URINARY ANTISPASMODICS*	15	1	16	93.75%
50 - ANTIEMETICS*	10	5	15	66.67%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	8	3	11	72.73%
34 - CALCIUM CHANNEL BLOCKERS*	5	6	11	45.45%
75 - MUSCULOSKELETAL THERAPY AGENTS*	3	4	7	42.86%
33 - BETA BLOCKERS*	6	0	6	100.00%
36 - ANTIHYPERTENSIVES*	4	2	6	66.67%
03 - MACROLIDES*	3	0	3	100.00%
39 - ANTIHYPERLIPIDEMICS*	2	1	3	66.67%
45 - RESPIRATORY AGENTS - MISC.*	2	1	3	66.67%
74 - NEUROMUSCULAR AGENTS*	1	2	3	33.33%
79 - MINERALS & ELECTROLYTES*	1	2	3	33.33%
97 - MEDICAL DEVICES AND SUPPLIES*	0	3	3	0.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	3	0	3	100.00%
01 - PENICILLINS*	0	2	2	0.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	2	0	2	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	1	2	50.00%
82 - HEMATOPOIETIC AGENTS*	0	2	2	0.00%
86 - OPHTHALMIC AGENTS*	1	1	2	50.00%
- COMPOUND	0	1	1	0.00%
02 - CEPHALOSPORINS*	1	0	1	100.00%
04 - TETRACYCLINES*	0	1	1	0.00%
11 - ANTIFUNGALS*	0	1	1	0.00%
55 - VAGINAL AND RELATED PRODUCTS*	0	1	1	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	0	1	100.00%
1Q23	**1,953**	**506**	**2.459**	
Percent of Total	**79.42%**	**20.58%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jan-23	16	80.00%	4	20.00%	20
Feb-23	18	66.67%	9	33.33%	27
Mar-23	20	62.50%	12	37.50%	32
1Q23	54	68.35%	25	31.65%	79

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
AIMOVIG	4	1	5	80.00%
AJOVY	2	1	3	66.67%
AMITIZA	1	1	2	50.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
ARIPIPRAZOLE	1	0	1	100.00%
BELSOMRA	0	1	1	0.00%
CABOMETYX	1	0	1	100.00%
COSENTYX SENSOREADY PEN	2	0	2	100.00%
CRESEMBA	1	0	1	100.00%
DAYVIGO	0	3	3	0.00%
DEXLANSOPRAZOLE	1	0	1	100.00%
DEXMETHYLPHENIDATE HYDROCHLORIDE ER	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
EMGALITY	3	0	3	100.00%
ENOXAPARIN SODIUM	2	0	2	100.00%
EPCLUSA	0	2	2	0.00%
EVRYSDI	1	0	1	100.00%
FENTANYL	1	0	1	100.00%
GENOTROPIN MINIQUICK	1	0	1	100.00%
HUMIRA PEN	1	0	1	100.00%
HUMIRA PEN-CD/UC/HS STARTER	1	0	1	100.00%
KINERET	1	0	1	100.00%
LINZESS	2	1	3	66.67%
LUBIPROSTONE	3	1	4	75.00%
LURASIDONE HYDROCHLORIDE	1	0	1	100.00%
MAVYRET	1	4	5	20.00%
METHYLPHENIDATE HYDROCHLORIDE CD	2	0	2	100.00%
MORPHINE SULFATE	1	0	1	100.00%
MORPHINE SULFATE ER	1	0	1	100.00%
MOUNJARO	0	1	1	0.00%
NORDITROPIN FLEXPRO	2	0	2	100.00%
NURTEC	4	0	4	100.00%
OPZELURA	1	0	1	100.00%
OZEMPIC	1	6	7	14.29%
PULMOZYME	1	0	1	100.00%
REPATHA SURECLICK	1	0	1	100.00%
SOFOSBUVIR/VELPATASVIR	1	1	2	50.00%
STELARA	1	0	1	100.00%
SYMPAZAN	0	1	1	0.00%
UBRELVY	1	0	1	100.00%
VRAYLAR	1	0	1	100.00%
XELJANZ XR	1	0	1	100.00%
XIFAXAN	0	1	1	0.00%
XOLAIR	1	0	1	100.00%
1Q23	**54**	**25**	**79**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 1/1/2023 – 3/31/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	16,410	$208,253.46	$12.69	6.87%
2	ANTICONVULSANTS, MISCELLANEOUS	12,729	$1,111,266.26	$87.30	5.33%
3	ATYPICAL ANTIPSYCHOTICS	10,059	$3,300,152.53	$328.08	4.21%
4	AMINOPENICILLIN ANTIBIOTICS	9,592	$139,638.57	$14.56	4.01%
5	RESPIRATORY AND CNS STIMULANTS	8,433	$749,950.65	$88.93	3.53%
6	SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,116	$479,489.88	$59.08	3.40%
7	AMPHETAMINES	7,983	$1,554,108.55	$194.68	3.34%
8	SECOND GENERATION ANTIHISTAMINES	7,544	$83,717.11	$11.10	3.16%
9	PROTON-PUMP INHIBITORS	6,957	$178,921.63	$25.72	2.91%
10	ADRENALS	6,762	$702,715.98	$103.92	2.83%
11	OPIATE AGONISTS	6,008	$178,623.27	$29.73	2.51%
12	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS, MISC	5,604	$74,878.84	$13.36	2.35%
13	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	4,573	$263,894.21	$57.71	1.91%
14	CONTRACEPTIVES	4,214	$128,819.76	$30.57	1.76%
15	SEL.SEROTONIN, NOREPI REUPTAKE INHIBITOR	4,162	$81,801.20	$19.65	1.74%
Total		**119,146**	**$9,236,231.90**	**$77.52**	**49.86%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 1/1/2023 – 3/31/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	10,059	$3,300,152.53	$328.08	4.21%
2	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	870	$2,714,388.54	$3,119.99	0.36%
3	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	389	$2,643,454.73	$6,795.51	0.16%
4	AMPHETAMINES	7,983	$1,554,108.55	$194.68	3.34%
5	CYSTIC FIBROSIS (CFTR) CORRECTORS	71	$1,548,061.54	$21,803.68	0.03%
6	INCRETIN MIMETICS	1,352	$1,193,612.26	$882.85	0.57%
7	ANTINEOPLASTIC AGENTS	330	$1,173,691.38	$3,556.64	0.14%
8	ANTICONVULSANTS, MISCELLANEOUS	12,729	$1,111,266.26	$87.30	5.33%
9	HEMOSTATICS	54	$1,077,463.38	$19,953.03	0.02%
10	RESPIRATORY AND CNS STIMULANTS	8,433	$749,950.65	$88.93	3.53%
11	ADRENALS	6,762	$702,715.98	$103.92	2.83%
12	LONG-ACTING INSULINS	1,422	$607,566.50	$427.26	0.60%
13	RAPID-ACTING INSULINS	1,390	$557,206.69	$400.87	0.58%
14	GI DRUGS, MISCELLANEOUS	444	$524,672.32	$1,181.69	0.19%
15	SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,116	$479,489.88	$59.08	3.40%
Total		**60,404**	**$19,937,801.19**	**$330.07**	**25.28%**

Total Rx Claims from 1/1/2023 – 3/31/2023	**238,959**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 1/1/2032 – 3/31/2023						
	Therapeutic Class Name	Drug Label Name	Total Rxs	Plan Paid Amount	Paid/Rx	% Total Claims
1	Penicillins	AMOXICILLIN	7,423	$96,544.82	$13.01	3.11%
2	Inhaled Bronchodilator	ALBUTEROL SULFATE/HFA	6,332	$202,433.52	$31.97	2.65%
3	Antidepressants	FLUOXETINE	5,777	$68,397.38	$23.56	2.42%
4	ADHD & Narcolepsy Medications	METHYLPHENIDATE	5,432	$319,021.95	$58.73	2.27%
5	Antidepressants	SERTRALINE	5,285	$66,441.18	$12.57	2.21%
6	ADHD & Narcolepsy Medications	VYVANSE	4,259	$1,418,271.83	$333.01	1.78%
7	Proton Pump Inhibitors	OMEPRAZOLE	4,188	$48,080.34	$11.48	1.75%
8	Antihistamines	CETIRIZINE	4,062	$42,200.56	$10.39	1.70%
9	Antidepressants	ESCITALOPRAM	3,814	$47,257.85	$12.39	1.60%
10	Antidepressants	TRAZODONE	3,702	$39,104.39	$10.56	1.55%
11	Anticonvulsants - 2nd Generation	GABAPENTIN	3,594	$59,120.71	$16.45	1.50%
12	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	3,453	$92,835.89	$26.89	1.45%
13	Thyroid Hormones	LEVOTHYROXINE	3,447	$46,355.86	$13.45	1.44%
14	Leukotriene Modulators	MONTELUKAST	3,197	$41,521.01	$12.99	1.34%
15	Antidepressants	BUPROPION	2,802	$52,669.98	$18.80	1.17%
16	Antiadrenergic Antihypertensives	CLONIDINE	2,593	$23,663.91	$9.13	1.09%
17	Atypical Antipsychotics	ARIPIPRAZOLE	2,366	$35,578.75	$15.04	0.99%
18	Opioid Agonists & Combos	HYDROCODONE BIT/AC	2,324	$34,412.90	$14.81	0.97%
19	ADHD & Narcolepsy Medications	GUANFACINE ER	2,244	$37,408.15	$16.67	0.94%
20	ACE Inhibitors & Combos	LISINOPRIL	2,204	$21,321.55	$9.67	0.92%
21	Penicillins	AMOXICILLIN/CLAVULANATE	2,157	$41,319.57	$19.16	0.90%
22	Statins & Combos	ATORVASTATIN	2,133	$24,603.48	$11.53	0.89%
23	Antianxiety Agents	HYDROXYZINE	2,122	$26,392.23	$12.44	0.89%
24	Antiemetics	ONDANSETRON ODT	2,117	$29,062.33	$13.73	0.89%
25	Macrolides	AZITHROMYCIN	1,992	$32,082.57	$16.11	0.83%
26	Atypical Antipsychotics	RISPERIDONE	1,935	$23,372.08	$12.08	0.81%
27	Cephalosporins	CEPHALEXIN	1,921	$30,551.71	$15.90	0.80%
28	Anticonvulsants - 2nd Generation	LAMOTRIGINE	1,889	$26,233.54	$13.89	0.79%
29	Glucocorticosteroids	PREDNISONE	1,867	$17,956.04	$9.62	0.78%
30	Antidepressants	FLUOXETINE	1,844	$21,417.51	$11.61	0.77%
31	Antianxiety Agents	BUSPIRONE	1,753	$22,169.28	$12.65	0.73%
32	Atypical Antipsychotics	QUETIAPINE	1,708	$21,885.97	$12.81	0.71%
33↓	Cephalosporins	CEFDINIR	1,697	$37,349.21	$22.01	0.71%
34	Antihistamines	LORATADINE	1,624	$17,439.81	$10.74	0.68%
35	Antidepressants	DULOXETINE	1,578	$24,949.11	$15.81	0.66%
36	Anticonvulsants - 2nd Generation	CLONAZEPAM	1,558	$17,250.49	$11.07	0.65%
37↓	Biguanides & Combos	METFORMIN L	1,544	$19,570.94	$12.68	0.65%
38	Nasal Steroids	FLUTICASONE PROPIONATE	1,510	$22,197.59	$14.70	0.63%
39	Muscle Relaxants & Combos	CYCLOBENZAPRINE HCL	1,507	$15,130.54	$10.04	0.63%
40	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,505	$22,474.46	$14.93	0.63%
41	-	COMPOUNDS	1,445	$36,136.14	$25.01	0.60%
42	Anticonvulsants - 2nd Generation	LEVETIRACETAM	1,402	$28,911.48	$20.62	0.59%
43	Proton Pump Inhibitors	PANTOPRAZOLE	1,375	$17,010.28	$12.37	0.58%
44	Anticonvulsants - 2nd Generation	TOPIRAMATE	1,349	$17,522.99	$12.99	0.56%
45	Calcium Channel Blockers	AMLODIPINE	1,333	$13,133.87	$9.85	0.56%
46	ADHD & Narcolepsy Medications	DEXMETHYLPHENIDATE	1,262	$49,498.91	$39.22	0.53%
47	Vitamins & Supplements	FOLIC ACID	1,258	$11,021.27	$8.76	0.53%
48↑	H-2 Antagonists	FAMOTIDINE	1,239	$26,782.46	$21.62	0.52%
49	Antidepressants	MIRTAZAPINE	1,234	$17,823.42	$14.44	0.52%
50	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	1,216	$13,978.55	$11.50	0.51%
	Total Top 50 Drugs		**127,572**	**$3,517,870.36**	**$27.58**	**53.39%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 1/1/2023 – 3/31/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	**HUMIRA/PEN/STARTER**	**159**	**$1,470,880.09**	**$9,250.82**	**0.07%**
2	ADHD & Narcolepsy Medications	VYVANSE	4,259	$1,418,271.83	$333.01	1.78%
3	Cystic Fibrosis	TRIKAFTA	57	$1,240,694.06	$21,766.56	0.02%
4	Chronic Inflammatory Disease	STELARA	54	$1,117,853.28	$20,700.99	0.02%
5	Atypical Antipsychotics	**INVEGA SUSTNA/TRNZA/HFYRA**	339	$1,060,249.99	$3,127.58	0.14%
6	Chronic Inflammatory Disease	DUPIXENT	285	$1,005,709.61	$3,528.81	0.12%
7	GLP-1 Receptor Agonists	OZEMPIC	793	$697,071.21	$879.03	0.33%
8	Atypical Antipsychotics	LATUDA	378	$490,878.00	$1,298.62	0.16%
9	Atypical Antipsychotics	VRAYLAR	391	$467,959.34	$1,196.83	0.16%
10	Atypical Antipsychotics	**ARISTADA/INITIO**	155	$428,532.21	$2,764.72	0.06%
11	Chronic Inflammatory Disease	**ENBREL/MINI/SURECLICK**	60	$399,411.41	$6,656.86	0.03%
12	Anticonvulsants - 2nd Generation	EPIDIOLEX	138	$383,134.17	$2,776.33	0.06%
13↑	Chronic Inflammatory Disease	**SKYRIZI/PEN**	17	$321,424.23	$18,907.31	0.01%
14	ADHD & Narcolepsy Medications	METHYLPHENIDATE	5,432	$319,021.95	$58.73	2.27%
15	Atypical Antipsychotics	REXULTI	251	$317,914.97	$1,266.59	0.11%
16↑	Antihemophilic Products	ADVATE	14	$312,180.42	$22,298.60	0.01%
17	Cystic Fibrosis	ORKAMBI	14	$307,367.48	$21,954.82	0.01%
18	Chronic Inflammatory Disease	**COSENTYX/SENSOREADY PEN**	44	$289,762.29	$6,585.51	0.02%
19	SGLT-2 Inhibitors & Combos	JARDIANCE	532	$286,363.02	$538.28	0.22%
20	Movement Disorder Drug Therapy	INGREZZA	36	$279,959.40	$7,776.65	0.02%
21	Chronic Inflammatory Disease	TALTZ	38	$269,406.80	$7,089.65	0.02%
22	HIV-Multiclass Combo	BIKTARVY	70	$255,251.08	$3,646.44	0.03%
23	Cystic Fibrosis	PULMOZYME	58	$234,368.74	$4,040.84	0.02%
24↓	Antihemophilic Products	NOVOSEVEN RT	3	$228,631.65	$76,210.55	0.00%
25	GLP-1 Receptor Agonists	TRULICITY	250	$225,895.74	$903.58	0.10%
26	Anti-Infective Agents - Misc.	XIFAXAN	83	$222,071.80	$2,675.56	0.03%
27	Glucagon-Like Peptide-2 (GLP-2) Analogs	GATTEX	5	$221,057.00	$44,211.40	0.00%
28	Growth Hormones	NORDITROPIN FLEXPRO	51	$215,241.91	$4,220.43	0.02%
29	Inhaled Bronchodilator	**ALBUTEROL SULFATE/HFA**	6,332	$202,433.52	$31.97	2.65%
30↑	Antihemophilic Products	XYNTHA SOLOFUSE	4	$181,123.80	$45,280.95	0.00%
31	Insulin	LANTUS SOLOSTAR	428	$171,428.57	$400.53	0.18%
32	Oral Anticoagulants	ELIQUIS	329	$158,577.27	$482.00	0.14%
33↑	Spinal Muscular Atrophy (SMA) Agent	EVRYSDI	9	$147,509.30	$16,389.92	0.00%
34	Antihemophilic Products	RECOMBINATE	3	$147,074.55	$49,024.85	0.00%
35	Inhaled Asthma/COPD Combo	ADVAIR HFA	404	$146,731.13	$363.20	0.17%
36	Insulin	TRESIBA FLEXTOUCH	295	$145,053.95	$491.71	0.12%
37	Pulmonary Arterial Hypertension	OPSUMIT	12	$141,483.44	$11,790.29	0.01%
38	Insulin	LEVEMIR/FLEXPEN/FLEXTOUCH	263	$131,068.04	$498.36	0.11%
39↑	Antihemophilic Products	ALPROLIX	7	$130,714.25	$18,673.46	0.00%
40	Atypical Antipsychotics	ABILIFY MAINTENA	52	$126,208.31	$2,427.08	0.02%
41	Bile Acid Synthesis Disorder Agents	CHOLBAM	6	$124,413.30	$20,735.55	0.00%
42	Insulin	INSULIN ASPART FLEXPEN	352	$120,957.15	$343.63	0.15%
43	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	200	$120,316.99	$601.58	0.08%
44↑	Oncology	KISQALI	8	$120,035.70	$15,004.46	0.00%
45↑	GLP-1 Receptor Agonists	MOUNJARO	122	$116,632.21	$956.00	0.05%
46	Irritable Bowel Syndrome (IBS) Agents	LINZESS	252	$116,629.41	$462.82	0.11%
47	Inhaled Steroids	FLUTICASONE PROPIONAT HF	663	$114,825.30	$173.19	0.28%
48↓	Chronic Inflammatory Disease	TREMFYA	9	$114,508.09	$12,723.12	0.00%
49↑	ADHD & Narcolepsy Medications	QELBREE	278	$114,095.55	$410.42	0.12%
50↑	ADHD & Narcolepsy Medications	JORNAY PM	294	$113,610.04	$386.43	0.12%
	Total Top 50 Drugs		**22,493**	**$17,491,993.55**	**$788.79**	**9.30%**

Old Business

Eucrisa Review

Time frame: 1/1/2023 to 3/31/2023

Drug Name	Total Rx	Paid Amount	Paid/ Rx	Avg Qty	Utilizer	Age Range
Opzelura cream 1.5% (ruxolitinib)	2	$3,874.28	$1,937.14	60gm/30 days	1	51
EUCRISA oint 2% (crisaborole)	41	$32,235.42	$786.26	72gm/28 days	36	0 – 56
pimecrolimus cream 1%	68	$13,256.34	$194.95	48gm/24 days	55	0 – 62
tacrolimus oint 0.03%	24	$1,360.88	$56.70	40gm/24 days	24	0 – 27
tacrolimus oint 0.1%	53	$5,383.60	$101.58	56gm/27 days	45	0 – 61

Red font denotes drug is on PA

Drug Name	Total Rx	Paid Amount	Paid/ Rx	Avg Qty	Utilizer	Age Range
EUCRISA oint 2% (crisaborole)	41	$32,235.42	$786.26	72gm/28 days	36	0 – 56

Utilizers per Age Range:

- 0 years 3
- 1 years 3
- 2 years 2
- 3 – 9 years 14
- 10 – 17 years 4
- 18 – 30 years 4
- 31 – 56 years 6

Utilizers by Gender:

Males 19
Female 17

Prescriber Taxonomy	Total Rx
Allergy & Immunology	*2*
Ambulatory Health Care Facilities/Clinic/Center/Urgent Care	3
Dermatology	*1*
Emergency Medicine	2
Family Practice	8
Nurse Practitioner	1
Nurse Practitioner, Family Health	2
Pediatrics	*6*
Pharmacist	1
Physician Assistant	1
Physician Assistant, Medical	1
Physician Assistant, Surgical	3
Preventive Medicine, Aerospace Medicine	1
Preventive Medicine, Obesity Medicine	1
Registered Nurse	3
Student in an Organized Health Care Education/Training Program/Student, Health Care	4
Surgery, Dermatologic	1

Diagnosis codes:

- Atopic dermatitis (L20-L20.9) – 17 utilizers
  - Males 10 Ages 0-2, 5-10, 18
  - Females 7 Ages 3, 4, 7, 17, 20-38

- Dermatitis, unspecified or allergic/contact dermatitis (L23.9, L25.9, L30.9) – 6 utilizers
  - Males 2 Ages 4, 13
  - Females 4 Ages 2, 9, 15, 37

- Other diagnosis of remaining 13 utilizers related to skin and subcutaneous tissue (L00-L99)
  - Male 3 yrs – Local infection of the skin and subcutaneous tissue, unspecified
  - Male 4 yrs – Impetigo – Male 4 years
  - Male 7 yrs – Impetigo, Local infection of skin and subcutaneous tissue
  - Female 0, 2, 8, 36, 46, 56 yrs – none
  - Male two 1, 6, 48 yrs – none

State A Eucrisa PA criteria:

Initial Authorization

- Must meet the following:
  - Member is 3 months of age or older AND one of the following:
    - ≥90 days of topical drug therapy with each of the following: corticosteroids AND calcineurin inhibitors (pimecrolimus or tacrolimus)
    - Prescriber has provided valid medical justification for the use of Eucrisa over topical corticosteroids, tacrolimus, and pimecrolimus

Reauthorization

- Must meet the following:
  - History of the requested agent within the past 365 days

State B Eucrisa PA criteria:

1. An FDA approved indication for treatment of mild-to-moderate atopic dermatitis (eczema); AND
2. Member must be at least 3 months of age or older; AND
3. Member must have a documented trial within the last six months for a minimum of two weeks that resulted in failure with a topical corticosteroid or topical calcineurin inhibitor (or have a contraindication or documented intolerance); AND
4. A quantity limit of one tube per 30 days will apply.
5. Initial approvals will be for the duration of one month. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Clinical Exceptions for Children Not Meeting Age Restriction:

1. Documented adverse effect, drug interaction, or contraindication to topical corticosteroids; OR
2. Atopic dermatitis of face or groin where prescriber does not want to use topical corticosteroids; OR
3. Prescribed by a dermatologist.

State C Eucrisa PA criteria:

Patient is ≥ 2 years; **AND**

1. Diagnosis of atopic dermatitis; **AND**
2. One of the following:
    a. Trial and failure of 2 topical corticosteroids AND 1 topical calcineurin Inhibitor (e.g., pimecrolimus)
    b. Trial and failure of either a topical corticosteroid OR a topical calcineurin inhibitor **AND** conditions preclude use of both classes:
        i. Conditions that preclude the use of steroids:
            - Treatment of sensitive areas (face, anogenital, skin folds)
            - Steroid Induced Atrophy
            - Long-term uninterrupted use
        ii. Conditions that preclude the use of topical calcineurin inhibitors:
            - Severely impaired skin barrier (Netherton Syndrome)
            - Risk/presence of new primary malignancy (e.g., skin cancer, lymphoma, or other lymphoproliferative disorders); **OR**

Patient is <2 years and greater than 3 months of age; **AND**

1. Diagnosis of atopic dermatitis; **AND**
2. Trial and failure of 2 topical corticosteroids unless patient has one of the following conditions that would preclude the use of steroids:
    a. Treatment of sensitive areas (face, anogenital, skin folds)
    b. Steroid Induced Atrophy
    c. Long-term uninterrupted use

State D Eucrisa PA criteria:

1. History of failure, contraindication, or intolerance to ONE topical corticosteroid [e.g., mometasone furoate, fluocinolone acetonide, fluocinonide] **AND**
2. One of the following:
    a. Patient is less than 2 years of age **OR**
    b. Patient is greater than or equal to 2 years of age and has history of failure, contraindication, or intolerance to ONE topical calcineurin inhibitor (e.g., pimecrolimus, tacrolimus)

Opzelura PA Criteria

1. Diagnosis of mild to moderate atopic dermatitis AND
2. Member is 12 years of age or older AND
3. One of the following:
    a. Greater than or equal to 3% body surface area involvement
    b. Involvement of sensitive body areas (e.g., face, hands, feet, scalp, groin)

AND

4. Greater than or equal to 90 days of topical drug therapy with **one** of the following: corticosteroids, pimecrolimus and/or tacrolimus, crisaborole AND
5. Member is not using concurrently with therapeutic biologics, other Janus kinase inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine AND
6. Requested quantity does not exceed 240 gm/30 days

Winlevi (clascoterone) PA

South Dakota Medicaid PA criteria – 12 months

1. Patient is 12 years old and older
2. Diagnosis of acne vulgaris
3. Patient has had a trial and failure of a generic topical acne agent in the last 120 days
    - benzoyl peroxide
    - tretinoin
    - clindamycin phosphate
    - erythromycin
    - sulfacetamide sodium
    - sulfacetamide sodium/sulfur

State A PA criteria:

1. Patient has a diagnosis of acne vulgaris
2. Patient is 12 years old and older
3. Member has tried and failed, allergies, contraindications, drug-drug interactions, or intolerable side effects to TWO of the following preferred products, each from different medication classes
    - Topical antibiotics: clindamycin 1% (gel, lotion, swab) erythromycin 2% (gel, solution), clindamycin 1.2%/benzoyl peroxide 5% gel;
    - Topical retinoids: Avita, Epiduo Forte, tretinoin cream, tretinoin gel 0.01%

Vtama (tapinarof) PA

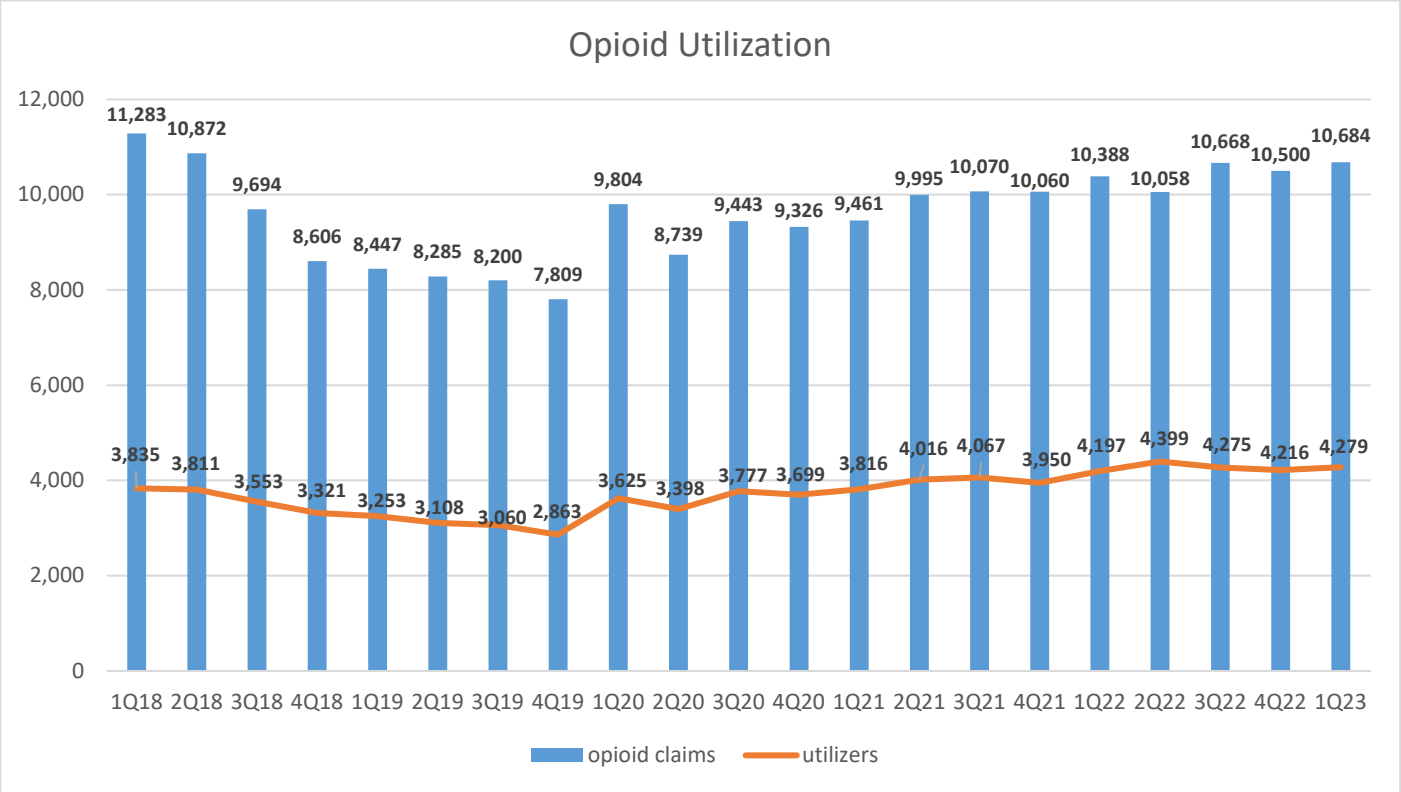
Initial authorization – 6 months

1. Patient is 18 years old and older
2. Diagnosis of plaque psoriasis
3. Minimum duration of a 4-week trial and failure, contraindication, or intolerance to ONE of the following generic topical therapies:
    - Corticosteroids (e.g., betamethasone, clobetasol)
    - Vitamin D analogs (e.g., calcitriol, calcipotriene)
    - Tazarotene
    - Calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
    - Anthralin
    - Coal tar
    - Combination topical therapy (e.g., vitamin D analog/corticosteroid)
4. Prescribed by or in consultation with a dermatologist

Reauthorization – 12 months

- Documentation of positive clinical response to therapy as evidenced by one of the following:
    - Reduction in the body surface area (BSA) involvement from baseline
    - Improvement in symptoms (e.g., pruritus, inflammation) from baseline

Opioid Summary



- 1Q2018 to 4Q2019 excludes IHS
- 1Q2020 to current includes IHS
- March 13, 2020 – Pandemic Closure

Opioid Initiatives:

1. June 1, 2018 – early refill threshold for controlled substance changed from 75% to 85%
2. July 1, 2028 – PA for more than one LAO and one SAO
3. August 1, 2018 – opioid Naïve PA (initial 7-day supply and 60 MED limit)
4. October 1, 2018 to October 1, 2019 – decrease from 300 MED to 90 MED (cancer diagnosis excluded)

Other Initiatives:

- Buprenorphine PA (Bunavail/Suboxone/Zubsolv/Subutex) and ST (Belbuca/Butrans) removed 10/14/2019
- Lidoderm PA removed 8/1/2020

Total Eligibility and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%

Opioid Utilization Snapshot

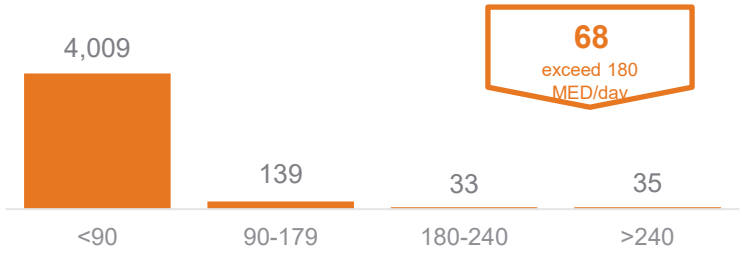
SDM 4Q2022
Sep 22 to Dec 22

Opioid Claims **10,500**
2.9% prescription claims filled for an opioid
0.9% higher than Medicaid FFS benchmark

Utilizers **4,216**
30.3% are high utilizers [1]
1.0% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy
50 opioid utilizing members with 3+ pharmacies

326 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

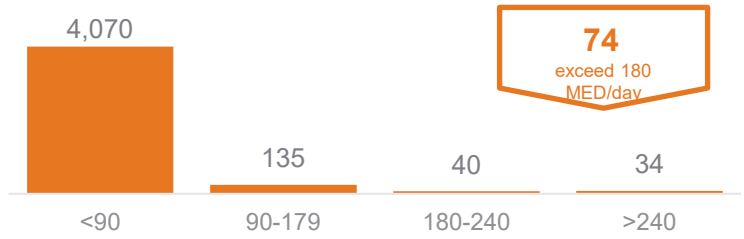
1Q2023
Dec 22 to Mar 23

Opioid Claims **10,684**
3.1% prescription claims filled for an opioid
0.9% higher than Medicaid FFS benchmark

Utilizers **4,279**
30.6% are high utilizers [1]
1.8% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy
66 opioid utilizing members with 3+ pharmacies

349 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

OPTUMRx®

[1]Defined as 3+ opioid scripts within 120 days period; [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization

SDM 1Q2023
Opportunities date range: Dec 2022 - Mar 2023
Benchmark: MEDICAID FEE FOR SERVICE

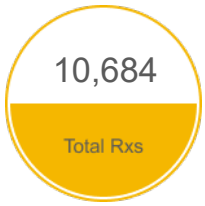
Utilizers: 4,279

2.9% of all Rx claims are filled for an Opioid

Opioid dependence can start in just a few days, and the risk of chronic opioid use increases with each additional day of opioid supplied, starting with the third day. Our Opioid Risk Management program, which includes point of sale, utilization management and retrospective drug utilization edits, are tightly aligned with CDC opioid prescribing guidelines which can help reduce exposure to excessive doses and prevent more members from transitioning from acute to chronic use.

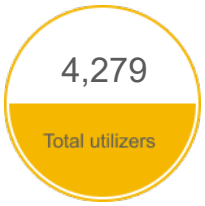
- Opioid prescriptions account for 2.9% of all prescriptions this period, which is 1.0% higher than the benchmark
- 1,309 high opioid utilizers were identified this period, which is 1.8% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
10.3%

Opioid utilizers

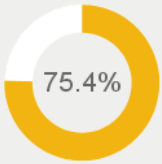


HIGH UTILIZERS
30.6%
1,309 high utilizers

1.8% over benchmark

High utilizers – Defined as 3+ opioid scripts within 120 day period

Claim breakdown



short acting opioids

75.4% of all opioid Rxs were filled for short acting opioids. **1,962** Rxs were for medication assisted therapy (MAT) and **188** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

MAT – Medication Assisted Therapy (buprenorphine, etc)
Overdose rescue therapy – opioid overdose reeversals w/naloxone
MME – relative potency of an opioid to a morphine dose

Utilizers by cumulative MED

74 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	4,070	135	40	34

MED – Morphine equivalent dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period

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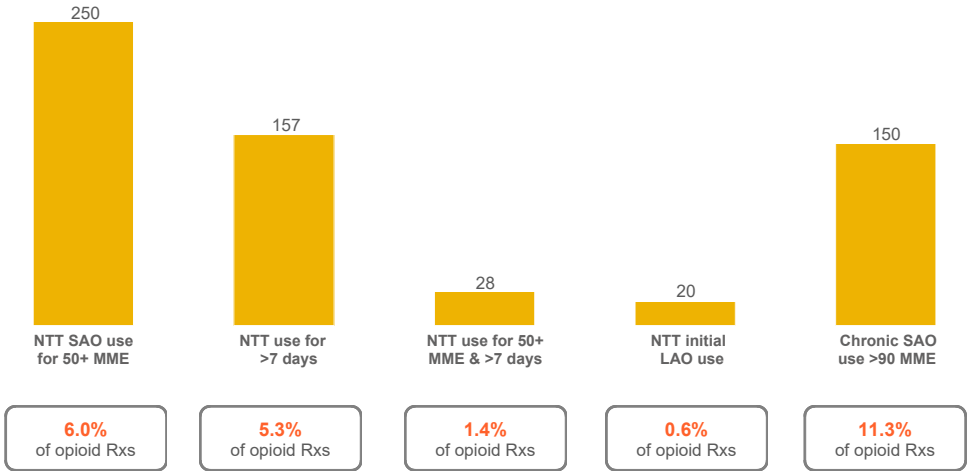
Opioid Opportunity Assessment

SDM 1Q2023
Opportunities date range: Dec 2022 - Mar 2023
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 10.3%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



NTT - view definition | SAO - view definition | LAO - view definition | MME - view definition

DID YOU KNOW?

66 opioid utilizing members use 3 or more pharmacies and 349 opioid utilizing members use 3 or more prescribers.

NNT - New to Therapy
SAO - Short Acting Opioid
LAO - Long Acting Opioid
MME - Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
762	544	737	N/A	109

Anticonvulsants –view definition

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New Business

Antidepressant PA Review

Time Frame: 10/1/2020–12/31/2020 vs 1/1/2023–3/31/2023

	4Q2020 (Reviewed at March 2021 meeting)			1Q2023		
Drug Name	**Total PAs**	**Approved**	**Denied**	**Total PAs**	**Approvals**	**Denials**
sertraline quantity limit: • 25mg, 1/day • 50mg, 1.5/day	12	QTY – 7 Reviews • 25mg, 1.5/day (2) • 25mg, 3/day (2) • 50mg, 2/day (2) • 50mg, 3/day PA – 1 Review • Solution	QTY – 3 Reviews • 25mg, 1.5/day • 25mg, 2/day • 50mg, 2/day PA – 1 Review • Solution	11	QTY – 7 Reviews • 25mg, 1.5/day • 25mg, 2/day • 25mg, 3/day • 50mg, 2/day • 50mg, 3/day • 50mg, 84/30 days one time titration • 50mg, 1/14 day then 2/day PA – 1 Review • Solution	QTY – 3 Reviews • 25mg, 1.5/day • 25mg, 2/day • 25mg, 3/day
citalopram quantity limit: • 10mg, 1/day • 20mg, 2/day • 40mg, 2/day	0			1		QTY – 1 • 20mg, 3/day
escitalopram quantity limit: • 5mg, 1/day • 10mg, 1.5/day • 20mg, 1.5/day • 5mg/5ml, 20mg/day	10	QTY – 2 Reviews • 5mg, 1.5/day • 20mg, 2/day PA – 1 Review • Solution	QTY – 7 Reviews • 5mg, 1.5/day (2) • 20mg, 2/day (3) • 20mg, 4/day • 5mg/ml – 40mg/day	7	QTY – 1 Review • 10mg- 2/day PA – 3 Reviews • Solution	QTY – 3 Reviews • 20mg, 2/day
fluoxetine quantity limit: • 10mg, **3**/day • 20mg, **3**/day • 40mg, **2**/day • 60mg, 1/day • 90mg, 1/week	18	QTY – 10 Reviews • 40mg, 2/day (10) PA – 3 Reviews • Solution (2) • Brand	QTY – 5 Reviews • 10mg, 3/day (2) • 20mg, 2/day • 40mg, 2/day (2)	6	PA – 4 Reviews • Solution	QTY – 2 Reviews • 90 mg, 2/week PA – 4 Reviews • Solution
paroxetine hcl quantity limit: • 10mg, 1/day • 20mg, 1/day • 30mg, 1/day • 40mg, 2/day	1	QTY – 1 Review • 10mg, 1.5/ day		2	QTY – 1 Review • 30mg, 2/day	QTY – 1 Review • 20mg, 1.5/day
paroxetine ER quantity limit: • 12.5mg, 1/day • 25mg, 2/day • 37.5mg, 1/day	2	PA – 1 Review	PA – 1 Review	1	PA – 1 Review	

Red font denotes drug is on PA/ST

	4Q2020 (Reviewed at March 2021 meeting)			1Q2023		
Drug Name	**Total PAs**	**Approved**	**Denied**	**Total PAs**	**Approvals**	**Denials**
venlafaxine ER quantity limit: • 37.5mg, 1/day • 75mg, 1/day • 150mg, 2/day	5	QTY – 4 Reviews • 75mg, 3/day only for 1 month • 37.5mg, 2/day (2) • 37.5mg, 3/day (2)	QTY – 1 Review • 75mg, 2/day	4		QTY – 4 Reviews • 37.5mg, 2/day (2) • 37.5mg, 3.33/day • 75mg, 2/day
desvenlafaxine ER quantity limit: • 50mg, 1/day • 100mg, 1/day	4	PA – 4 Reviews		5	PA – 2 Reviews	PA – 3 Reviews
duloxetine quantity limit: • 20mg, **3**/day • 30mg, **3**/day • 60mg, **2**/day	34	QTY – 28 Reviews • 30mg, 3/day (5) • 60mg, 2/day (23)	QTY – 6 Reviews • 30mg, 3/day (2) • 30mg, 4/day • 60mg, 2/day (3)	0		
fluvoxamine quantity limit: • 50mg, **3**/day • 100mg, 3/day • 100mg XR, 1/day • 150mg XR, 1 day	1	QTY – 1 Review • 50mg, 3/day		0		
olanzapine/ fluoxetine quantity limit: • 1/day	1	PA – 1 Review		0		
Wellbutrin XL	2	PA – 2 Reviews		1	PA – 1 Review • Brand 300mg XL	
bupropion ER/XL quantity limit: • 150mg, 12HR 2/day • 150mg, 24HR 1/day • 300mg, 24HR 1/day • 450mg, 24HR 1/day	6	QTY – 2 Reviews • 150mg, 2/day • 300mg, 2/day	QTY 4 Review • 150mg, 2/day • 150mg, 3/day	5	QTY – 4 Reviews • 150mg XL, 3/day (2) • 150mg XL, 53/30 days PA – 1 Review RTS* • 450mg XL	QTY – 1 Review • 150mg XL, 3/day bc 450mg XL is commercially available
mirtazapine quantity limit: • 15mg, 1/day • 30mg, 1/day • 45mg, 1/day	3	QTY – 1 Review • 15mg, 1.5/day	QTY – 2 Reviews • 30mg, 2/day • 45mg, 1.5/day	1	QTY – 1 Review • 15mg, 2/day	
mirtazapine ODT quantity limit: • 15mg, 1/day • 30mg, 1/day • 45mg, 1/day	0			2	PA – 2 Reviews	

Red font denotes drug is on PA/ST
*RTS – Refill-too-soon

Time frame: 1/1/2023 to3/31/20203

	4Q2020 (Reviewed at March 2021 meeting)				1Q2023			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
citalopram cap/tab/sol	1,056	$9,312.03	$8.88	466	1,039	$9,423.38	$9.07	477
escitalopram tab	2,632	$32,179.93	$12.23	1,162	3,824	$45,749.68	$11.96	1,733
Lexapro tab	10	$3,981.58	$398.16	4	6	$2,499.99	$416.67	3
escitalopram solution	0				23	$1,893.34	$82.32	10
fluoxetine cap	4,720	$63,686.78	$13.49	1,910	5,028	$51,354.23	$10.22	2,106
fluoxetine cap 90 mg	21	$2,651.48	$126.26	8	22	$2,577.66	$117.17	7
fluoxetine tab	453	$11,384.88	$25.13	236	608	$9,949.38	$16.36	296
fluoxetine solution	112	$6,882.19	$61.45	49	189	$7,709.03	$40.79	90
fluvoxamine tab	51	$1,345.45	$26.91	19	33	$746.23	$22.61	13
fluvoxamine cap ER	1	$194.40	194.40	1	4	$706.71	$176.71	1
paroxetine tab	353	$3,831.63	$10.85	138	413	$4,635.36	$11.22	177
paroxetine ER	21	$1,009.99	$48.09	9	15	$547.53	$36.50	7
paroxetine mesylate	1	$141.39	$141.39	1	4	$486.21	$121.55	2
paroxetine susp	0				3	$3,997.29	$1,332.43	1
sertraline tab	4,215	$49,273.58	$11.69	1,842	5,242	$59,928.61	$11.43	2,337
sertraline **cap**	0				31	$4,747.75	$156.38	15
sertraline conc sol	42	$1,853.01	$44.12	17	42	$2,005.86	$47.76	17
olanzapine-fluoxetine	9	$3,811.95	$423.55	5	4	$1,022.24	$255.56	2
Desvenlafax ER tab	3	$376.80	$125.60	1	8	$1,137.86	$142.23	5
desvenlafax suc ER tab	211	$6,178.10	$29.28	80	465	$10,906.62	$23.46	184
Pristiq	6	$2,437.92	$406.32	2	0			
venlafaxine tab	97	$1,549.29	$15.97	44	129	$1,707.24	$13.23	56
venlafaxine ER tab	48	$7,448.29	$155.17	23	89	$5,338.53	$59.98	40
venlafaxine ER cap	1,024	$15,819.27	$15.45	375	1,243	$17,480.62	$14.06	461
Effexor XR cap	10	$10,087.86	$1,008.79	3	5	$6,608.17	$1,321.63	2
duloxetine	1,629	$26,594.68	$16.33	608	2,234	$34,028.95	$15.23	884
Cymbalta	3	$1,496.95	$498.98	1	0			
Fetzima (levomilnacipran)	17	$6,832.54	$401.91	6	12	$6,390.59	$532.55	4
bupropion tab	110	$2,140.23	$19.46	51	109	$1,864.17	$17.10	59
bupropion tab SR	392	$6,404.13	$16.34	173	355	$5,141.40	$14.48	187
bupropion tab XL	1,614	$33,620.82	$20.83	657	2,392	$46,662.33	$19.51	1,036
Wellbutrin tab XL 300mg	5	$9,333.56	$1,866.71	2	5	$11,203.84	$2,246.17	2
Forfivo XL	0				4	$1,800.72	$450.18	2
mirtazapine	1,218	$17,179.92	$14.11	479	1,243	$17,927.51	$14.42	506
mirtazapine ODT	17	$455.21	$26.78	7	12	$286.37	$23.86	7
mirtazapine solution	0				0			
vilazodone	0				216	$12,266.32	$56.79	83
Viibryd	174	$43,936.72	$252.17	64	11	$1,709.40	$155.40	5
Trintellix (vortioxetine)	140	$50,822.31	$363.02	46	134	$54,906.65	$409.75	50

Red font denotes drug is on PA/ST

Asthma Guidelines

Overview of the 2020 updates to the NIH Asthma Management Guidelines: Key points for pediatrics

There were 19 recommendations, 3 are strong and 2 are based on evidence with high certainty

STRONG EVIDENCE-BASED RECOMMENDATIONS:

1. **SMART** (single maintenance and reliever therapy) including a **single inhaler with inhaled corticosteroid (ICS) + long acting ß$_2$-agonist** (LABA, such as formoterol) should be used for both **daily use AND rescue therapy** for all children ≥4 yr with moderate to severe persistent asthma. This is proven to be more effective than ICS alone. It is STROGNLY recommended over higher dose ICS. This strategy is proven to be superior to:
    1. Higher dose ICS + short acting ß$_2$-agonist (SABA) or
    2. Same dose ICS + LABA + SABA for acute exacerbations

    SMART + SABA may be used for quick relief therapy in patients ≥4 yr with moderate to severe persistent asthma

2. **Fractional exhaled nitric oxide** can indirectly measure inflammation in the airway but should not be used to *predict asthma* or exacerbations in children < 5yo. It can be used with monitoring and management strategies.

HIGH DEGREE OF EVIDENCE

1. I**ntermittent ICS + SABA for 7-10 day course** may be used at the start of viral URI or other triggers in **children 0-4 years** of age **with recurrent wheezing but no daily symptoms** between triggers (intermittent wheezing – no diagnosis yet)
2. SMART is preferred as daily controller and reliever (as above) for quick relief therapy in patients over 12 years of age with moderate to severe persistent asthma

Asthma Utilization

Time Frame: 1/1/2023–3/31/2023 to identify members taking ICS without albuterol claims (667 members)
Then pulled utilization from 4/1/2022 to 5/21/2023 to search for any respiratory drug claims

- 116 members only using ICS (no albuterol/levalbuterol and LABA)
- 255 members using ICS and albuterol/levalbuterol (no LABA)
- 52 members ICS and LABA (no albuterol/levalbuterol)

SABA short-acting beta$_2$- agonist	ICS inhaled corticosteroid	LABA long acting beta$_2$-agonist	LABA/ICS combo
albuterol HFA • ProAir HFA • ProAir Digihaler • ProAir RespiClick • Proventil HFA • Ventolin HFA levalbuterol HFA • Xopenex HFA albuterol nebulization albuterol oral tab albuterol syrup levalbuterol nebulization terbutaline oral tabs & inj	beclomethasone • QVAR Redihaler budesonide • Pulmicort Flexhaler • Pulmicort Respules ciclesonide • Alvesco fluticasone propionate • ArmonAir Digihaler • Arnuity Ellipta • Flovent Diskus • Flovent HFA mometasone • Asmanex HFA • Asmanex Twisthaler	arformoterol • Brovana formoterol • Perforomist olodaterol • Striverdi Respimat salmeterol • Serevent Diskus	budesonide/formoterol • Symbicort fluticasone/salmeterol • Advair Diskus • Advair HFA • Wixela Inhub • AirDuo RespiClick fluticasone/vilanterol • Breo Ellipta mometasone/formoterol • Dulera

Sotyktu (deucravacitinib)

-for treatment of moderate-to-severe plaque psoriasis, 6mg tablet once daily

South Dakota Medicaid general psoriasis PA criteria:

1. Diagnosis of chronic plaque psoriasis **AND**
2. Patient is ≥ XX years of age **AND**
3. Prescribed by or in consultation with a dermatologist **AND**
4. The medication will not be used in combination with another biologic agent **AND**
5. Patient has had an inadequate response to, intolerance to, or contraindication to conventional therapy with at least one of the following: phototherapy or one or more oral systemic treatments (i.e., methotrexate, cyclosporine, acitretin, sulfasalazine, calcipotriene, tazarotene, corticosteroid)

State A PA criteria:

1. Member is 18 years od
2. Diagnosis of psoriasis
3. Previous trial and failure of at least two other targeted immunomodulators
4. Patient does not have a history of targeted immunomodulator

State B PA criteria:

1. Medical records confirming diagnosis of moderate to severe plaque psoriasis
2. Medical records confirming one of the following:
    a. At least 3% body surface area (BSA) involvement
    b. Severe scalp psoriasis
    c. Palmoplantar (i.e., palms, soles), facial, or genital involvement
3. Minimum duration of a 4-week trial and failure, contraindication, or intolerance to one of the following topical therapies
    a. corticosteroids (e.g., calcitriol, calcipotriene)
    b. tazarotene
    c. calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
    d. anthralin
    e. coal tar
4. Prescribed by or in consultation with a dermatologist
5. Trial and failure of preferred product
6. Not used in combination with other potent immunosuppressants (e.g., azathioprine, cyclosporine)

Reauthorization

1. Submission of medical records confirming positive clinical response to therapy as evidenced by one of the following:
    a. Reduction of body surface area (BSA) involvement from baseline
    b. Improvement in symptoms (e.g., pruritus, inflammation) from baseline

State C PA criteria:

1. Diagnosis of plaque psoriasis
2. Trial and failure, contraindication, or intolerance to at least one topical treatment from the following:
    a. corticosteroid
    b. calcipotriene
    c. tazarotene
3. Trial and failure, contraindication, or intolerance to two preferred immunomodulators with the same indication.

Optum Rx®

Therapeutic Class Overview

Immunomodulators

Introduction

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), alopecia areata, and uveitis (UV), as well as several less common conditions. Immunomodulators that treat CD and UC are covered in a separate review (Inflammatory Bowel Disease Agents). In addition, immunomodulators that treat atopic dermatitis are covered in a separate review (Atopic Dermatitis Agents).
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as numerous biosimilar TNF inhibitors: Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Yusimry (adalimumab-aqvh), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda). Other immunomodulators targeting different cells and cytokines in the inflammatory and immune process are also FDA-approved. These include:
  - Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell.
  - Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells.
    - Biosimilar products have also been approved: Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx).
  - Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor.
  - Kineret (anakinra), which targets the IL-1 receptor.
  - Ilaris (canakinumab), which binds to the IL-1ß receptor.
  - Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines.
  - Cosentyx (secukinumab) and Taltz (ixekizumab), which bind and neutralize IL-17A.
  - Siliq (brodalumab), an IL-17 receptor antagonist.
  - Tremfya (guselkumab), Skyrizi (risankizumab), and Ilumya (tildrakizumab-asmn), which are IL-23 antagonists.
- Oral immunomodulator agents on the market include:
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Rinvoq (upadacitinib), and Olumiant (baricitinib), which target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
  - Otezla (apremilast), a small-molecule phosphodiesterase 4 (PDE-4) inhibitor.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but not discussed in detail. These include:
  - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); 4) familial Mediterranean fever (FMF); and 5) adult-onset Still's disease.
  - Kineret for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) and CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID).
  - Actemra for giant cell arteritis (GCA), cytokine release syndrome (CRS), and systemic sclerosis-associated interstitial lung disease (SSc-ILD).
  - Cimzia, Cosentyx, Rinvoq, and Taltz for non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
  - Orencia for prophylaxis of acute graft-versus-host disease (GVHD).
  - Otezla for treatment of adults with oral ulcers associated with Behçet disease.
  - Cosentyx (secukinumab) for enthesitis-related arthritis in patients 4 years and older.
- Rituxan and biosimilar products are also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris. These indications will not be discussed in this review.

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- Olumiant (baricitinib) has been approved for the treatment of COVID-19 in hospitalized patients requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Information on COVID-19-related indications will not be addressed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2021*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, including FCAS and MWS, DIRA, and recurrent pericarditis is also not included in this review (*Arcalyst prescribing information 2021*).
- Although FDA-approved, the launch plans for many biosimilar drugs are pending and may be delayed; therefore, these agents are not currently included in this review (Purple Book: Database of Licensed Biological Products 2023).
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*	Type of Agent
Actemra (tocilizumab)	-	Human monoclonal antibody targeting the IL-6 receptor
Amjevita (adalimumab-atto)	N/A‖	TNFα inhibitor
Avsola (infliximab-axxq)	N/A*	TNFα inhibitor
Cimzia (certolizumab)	-	TNFα inhibitor
Cosentyx (secukinumab)	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	-‡	sTNFR fusion protein, TNFα inhibitor
Humira (adalimumab)	-†	TNFα inhibitor
Ilaris (canakinumab)	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	N/A*	TNFα inhibitor
Kevzara (sarilumab)	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	-	IL-1 receptor antagonist
Olumiant (baricitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	-	Small-molecule phosphodiesterase 4 inhibitor
Riabni (rituximab-arrx)	N/A§	Anti-CD20 monoclonal antibody
Remicade (infliximab)	-*	TNFα inhibitor
Renflexis (infliximab-abda)	N/A*	TNFα inhibitor
Rinvoq (upadacitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Rituxan (rituximab)	-§	Anti-CD20 monoclonal antibody
Ruxience (rituximab-pvvr)	N/A§	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/Simponi Aria (golimumab)	-	TNFα inhibitor
Skyrizi (risankizumab-rzaa)	-	Human monoclonal antibody to IL-23
Stelara (ustekinumab)	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	-	Human monoclonal antibody to IL-23 cytokine
Truxima (rituximab-abbs)	N/A§	Anti-CD20 monoclonal antibody

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Drug	Alternative Available (same molecular entity)*	Type of Agent
Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib)	-	Small molecule Janus kinase (JAK) inhibitor

**For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
*Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Avsola (infliximab-axxq) have been FDA-approved as biosimilar agents to Remicade (infliximab).
†Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), and Yusimry (adalimumab-aqvh have been FDA-approved as biosimilars to Humira (adalimumab). Cyltezo (adalimumab-adbm) is the only biosimilar product in this review that is designated interchangeable with its reference product, Humira (adalimumab). Further information regarding adalimumab biosimilars will be added to this review as these products launch.
‡Erelzi (etanercept-szzs) and Eticovo (etanercept-ykro) have been FDA-approved as biosimilars to Enbrel (etanercept). Further information on etanercept biosimilars will be included in this review as these products launch.
§Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx) have been FDA-approved as biosimilar agents to Rituxan (rituximab).
ǂAmjevita (adalimumab-atto) has been FDA-approved as biosimilar to Humira (adalimumab).

(Drugs@FDA, 2023; Purple Book: Database of Licensed Biological Products 2023)

Indications

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: oral ulcers associated with Behçet disease, CAPS, CRS, ERA, FMF, GCA, prophylaxis of acute GVHD, HIDS/MKD, NRAS, and TRAPS)***

Drug	Rheumatoid Arthritis (RA)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Hidradenitis Suppurativa (HS)	Uveitis (UV)	Alopecia areata
Actemraˠ (tocilizumab)	✔ *	✔ **	✔ **						
Amjevita (adalimumab-atto)	✔ ‡‡		✔ ∫	✔ ‡	✔ ∫∫	✔			
Avsola (infliximab-axxq)	✔ ⊥			✔ ‡‡‡	✔	✔			
Cimzia~~ (certolizumab)	✔			✔ ‡	✔	✔			
Cosentyx~~,▼▼▼ (secukinumab)				✔ ‡	✔ **	✔			

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Drug	Rheumatoid Arthritis (RA)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Hidradenitis Suppurativa (HS)	Uveitis (UV)	Alopecia areata
Enbrel (etanercept)	✔ †		✔ **	✔ ‡	✔ †	✔			
Humira (adalimumab)	✔ ‡‡		✔ ∫	✔ ‡	✔ ∫∫	✔	✔ ↑	✔ ▼	
Ilaris” (canakinumab)		✔ **							
Ilumya (tildrakizumab-asmn)				✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥			✔ ‡‡‡	✔	✔			
Kevzara (sarilumab)	✔ *								
Kineret▼▼ (anakinra)	✔ ∞								
Olumiant (baricitinib)	✔ *,⌂⌂								✔ ⌂⌂⌂⌂
Orencia∞∞∞ (abatacept)	✔ ∞∞		✔ ⌂		✔				

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Otezla~~~ (apremilast)				✔ △△△	✔				
Remicade (infliximab)	✔ ⊥			✔ ‡‡‡	✔	✔			
Renflexis (infliximab-abda)	✔ ⊥			✔ ‡‡‡	✔	✔			
Riabni'''' (rituximab-arrx)	✔ ǂ								
Rinvoq (upadacitinib)	✔ *,△△				✔ *,△△	✔ *,△△			
Rituxan''' (rituximab)	✔ ǂ								
Ruxience (rituximab-pvvr)	✔ ǂ								
Siliq (brodalumab)				✔ ǂǂ					
Simponi (golimumab)	✔ ┤				✔ ┤┤	✔			

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Simponi Aria (golimumab)	✔ †		✔ **		✔ **	✔			
Skyrizi (risankizumab-rzaa)				✔ ‡	✔				
Sotyktu (deucravacitinib)				✔ ‡					
Stelara (ustekinumab)				✔ ‡	✔ ▼▼▼▼				
Taltz~~ (ixekizumab)				✔ ‡	✔	✔			
Tremfya (guselkumab)				✔ ‡	✔				
Truxima (rituximab-abbs)''''	✔ ǂ								
Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib)	✔ *,⌂⌂		✔ *,**,⌂⌂		✔ *,⌂⌂	✔ *,⌂⌂			

ŸActemra is also indicated for treatment of giant cell arteritis in adults, chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years, and adults with systemic sclerosis-associated interstitial lung disease.

*Patients with moderately to severely active RA who have had an inadequate response or intolerance to ≥ 1 disease-modifying anti-rheumatic drugs (DMARDs) (Actemra, Kevzara) or ≥ 1 tumor necrosis factor (TNF) antagonists (Olumiant, Rinvoq, Xeljanz).

**Patients 2 years and older.

†In combination with methotrexate (MTX) or used alone.

‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy; Taltz and Cosentyx, which are indicated for the treatment of patients 6 years and older with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy; Stelara, which is indicated for the treatment of patients 6 years and older with moderate to severe PsO.

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‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of juvenile idiopathic arthritis (JIA) for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼ Treatment of non-infectious intermediate, posterior and panuveitis in adult and pediatric patients 2 years of age or older.
↑ Treatment of moderate to severe hidrandenitis suppurative in patients 12 years of age or older.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID), and for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA).
"Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; familial Mediterranean fever (FMF) in adult and pediatric patients; and adult-onset Still's disease.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active polyarticular juvenile idiopathic arthritis (PJIA). May be used as monotherapy or with MTX.
⊥In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
'''Rituxan and Ruxience are also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA); Rituxan is additionally indicated for pemphigus vulgaris.
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1 TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┼ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┼┼ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
┼┼┼ In combination with nonbiologic DMARDs.
~~Cimzia, Cosentyx, Rinvoq, and Taltz are also indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
~~~Otezla also indicated for treatment of adults with oral ulcers associated with Behçet disease.
''''Truxima and Riabni are also indicated for adults with NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
***Ruxience is indicated for NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
▼▼▼Cosentyx is also indicated for treatment of active ERA in patients 4 years of age and older.
∞∞∞Indicated for prophylaxis of acute graft vs host disease in combination with a calcineurin inhibitor and MTX in adults and pediatric patients ≥ 2 years undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor.
⌂⌂ Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
⌂⌂⌂ Indicated for the treatment of adult patients who are candidates for phototherapy or systemic therapy.
⌂⌂⌂⌂ Indicated for severe alopecia areata in adults.
▼▼▼▼ Indicated for patients 6 years or older with active PsA.

(*Prescribing information: Actemra 2022; Amjevita 2022; Avsola 2021; Cimzia 2022; Cosentyx 2021; Enbrel 2022; Humira 2021; Ilaris 2020; Ilumya 2022; Inflectra 2022; Kevzara 2018; Kineret 2020; Olumiant 2022; Orencia 2021; Otezla 2021; Remicade 2021; Renflexis 2022; Riabni 2022; Rinvoq 2022; Rituxan 2021; Ruxience 2021; Siliq 2020; Simponi 2019; Simponi Aria 2021; Skyrizi 2022; Sotyktu 2022; Stelara 2022; Taltz 2022; Tremfya 2020; Truxima 2022; Xeljanz/Xeljanz XR/Xeljanz oral solution 2022)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

Clinical Efficacy Summary

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).

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- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- Amjevita (adalimumab-atto) was compared with US-licensed Humira in patients with moderate to severe RA despite treatment with methotrexate in a randomized, double-blind, equivalence study *(Cohen et al 2017)*. Patients were randomized to Amjevita or adalimumab (40 mg) every 2 weeks. At week 24, the primary endpoint of ACR20 occurred in 74.6% and 72.4% of patients treated with Amjevita or Humira, respectively; because the 90% CI for risk ratio of ACR lay between 0.738 and 1.355, biosimilarity of Amjevita to Humira was established.
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean

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Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; p < 0.001) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [p < 0.001]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
  - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al 2010).
  - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
  - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 (p < 0.001). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well (p < 0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; p < 0.0296 for 4 mg/kg and p < 0.0082 for 8 mg/kg) (*Smolen et al 2008*).
  - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful

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improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008*).
  - RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).
- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be noninferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A Phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2018).*
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases

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in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). Treatment effects were maintained through month 24 in the ORAL Scan trial, with an ACR 20 response rate of 50.5% and 58.3% for tofacitinib 5 mg and 10 mg twice daily, respectively (*van der Heijde et al 2019[a]*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, Phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). Disease control with baricitinib was maintained at 3 years follow up with no new safety signals (*Smolen et al 2021*).
- Approval of Rinvoq (upadacitinib) was based on clinical trials from the SELECT program in patients with RA. In SELECT-EARLY (n = 947), 52% of MTX-naïve patients treated with upadacitinib 15 mg daily achieved ACR 50 vs 28% treated with MTX at week 12, and at week 24, significantly more patients treated with upadacitinib 15 mg daily had no radiographic progression (87.5% vs 77.7%; $p < 0.01$) *(van Vollenhoven et al 2018)*. In SELECT-MONOTHERAPY (n = 648), 68% of patients with an inadequate response or intolerance to MTX (MTX-IR) treated with upadacitinib 15 mg daily achieved ACR 20 vs 41% treated with continued MTX at week 14 *(Smolen et al 2019)*. In SELECT-COMPARE, which evaluated MTX-IR patients (n = 1629), ACR 20 was significantly more frequent with upadacitinib 15 mg daily vs placebo and vs adalimumab at week 12 (70.5% vs 36.4% and 63%, respectively; $p < 0.001$ and $p < 0.05$) and at week 26 (67.4% vs 35.6% and 57.2%, respectively; $p <0.001$ and $p <0.01$). At week 26, significantly more patients treated with upadacitinib had no radiographic progression vs placebo (83.5% vs 76.0%; $p < 0.001$) *(Fleischman et al 2018)*. Differences between upadacitinib and adalimumab were maintained for up to 3 years of treatment (*Fleischmann et al 2022*). In SELECT-BEYOND (n = 499), 65% of biologic-IR patients treated with upadacitinib 15 mg daily plus conventional DMARDs achieved ACR 20 vs 28% treated with placebo plus conventional DMARDs at week 12 ($p <0.0001$) *(Genovese et al 2018)*. A network meta-analysis of the SELECT trials found that upadacitinib plus MTX was more effective than MTX alone, and upadacitinib 15 mg plus MTX was most likely to achieve the best ACR 20 response rate (followed by upadacitinib 30 mg plus MTX, adalimumab 40 mg plus MTX, upadacitinib 30 mg, upadacitinib 15 mg, and MTX, in order) (*Song and Lee 2020*).
- A meta-analysis investigated the relative efficacy and safety profiles of tofacitinib, baricitinib, upadacitinib, and filgotinib (not approved in the US) in patients with active RA refractory to biologics (*Lee et al 2021*). The ranking probability based on the SUCRA suggested that upadacitinib had the highest probability of being the best treatment for achieving ACR20, followed by filgotinib (200 mg), baricitinib, filgotinib (100 mg), and tofacitinib. For achievement of ACR50, the SUCRA suggested that baricitinib was the best treatment, followed by filgotinib (200 mg), tofacitinib, upadacitinib, and filgotinib

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(100 mg). Tofacitinib was superior to filgotinib (100 mg) and upadacitinib for achievement of ACR70. Tofacitinib and filgotinib (200 mg) showed a significantly lower serious adverse event rate than upadacitinib.

- A 24-week, Phase 3, double-blind trial explored the efficacy of upadacitinib compared with abatacept in 612 patients with RA. The mean change in the Disease Activity Score for 28 joints based on C-reactive protein (DAS28-CRP) was -2.52 in the upadacitinib group and -2.00 in the abatacept group from baseline to week 12 (difference, -0.52 points; 95% CI, -0.69 to -0.35; p < 0.001 for noninferiority; p < 0.001 for superiority). Additionally, 30% of patients in the upadacitinib group and 13.3% of patients in the abatacept group achieved remission (difference, 16.8%; 95% CI, 10.4 to 23.2; p < 0.001 for superiority) (*Rubbert-Roth et al 2020*).
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
  - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized Phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints were also very similar between the 2 groups.
  - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Avsola (infliximab-axxq) was evaluated and compared to Remicade (infliximab) in 558 patients in a double-blind, multicenter, randomized equivalence trial (*Genovese et al 2020*). The primary endpoint, ACR 20 at week 22, was achieved by 68.1% and 59.1% of patients in the Avsola and Remicade groups, respectively (TD, 9.37%; 90% CI, 2.67% to 15.96%). The upper bound exceeded the pre-specified equivalence criteria by 0.96% such that superiority could not be ruled out statistically. In a post hoc analysis with adjustment for imbalances in baseline factors, the CI was narrowed (90% CI, 0.75% to 13.62%). Secondary endpoints were also very similar between the 2 groups.
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life (QoL).
- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
  - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified noninferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was noninferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high

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percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).

- Truxima (rituximab-abbs) was compared to Rituxan (rituximab) in 372 patients in a double-blind, multicenter, randomized Phase 3 trial (*Park et al 2018*). The primary efficacy endpoint, change from baseline in DAS28 based on C-reactive protein (CRP) at week 24, was -2.13 and -2.09 for Truxima and Rituxan, respectively (TD, -0.04; 95% CI, -0.29 to 0.21). Equivalence was demonstrated between the 2 products. Secondary endpoints were also very similar between the 2 groups.
  - In an extension of this study, 330 patients received a second 24-week course of their assigned study drug (Truxima or Rituxan) (Suh et al 2019). Mean change in DAS28-CRP from baseline to week 48 was similar between groups (-2.7 and -2.6 for Truxima and Rituxan, respectively). ACR 20/50/70 responses were also similar between groups at week 48.
  - After week 48, 295 patients entered a second extension phase that continued until week 72; during this extension phase, patients who were previously receiving Truxima or Rituxan (European Union formulation) received Truxima, while patients who were previously receiving Rituxan (United States formulation) were randomized 1:1 to continue receiving Rituxan (United States formulation) or switch to Truxima (Shim et al 2019). All patients experienced similar improvements in disease activity parameters, including DAS28 and ACR response rates. Switching from Rituxan to Truxima did not result in any clinically meaningful efficacy differences.
- Riabni (rituximab-arrx) was compared to Rituxan (rituximab) in a double-blind, multicenter, randomized controlled trial (*Burmester et al 2020*). The primary efficacy endpoint, change from baseline in DAS28-CRP at week 24, was -2.197 and -2.125 for Riabni and Rituxan, respectively (difference between means, -0.02%; 90% CI, -0.225 to 0.264). Equivalence was demonstrated between the 2 products.
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
  - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-*

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Sarabia et al 2005). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).

- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).
- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).
- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
  - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
  - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
  - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016[b]*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.

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  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).
- A Bayesian network meta-analysis of 5 randomized trials (n = 1,547) examined the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib (not approved in the U.S.) and peficitinib (not approved in the U.S.) in patients with RA. The ranking probability based on SUCRA revealed the following agents with the highest probability to achieve the ACR 20 response rate: peficitinib 150 mg (highest probability) followed by peficitinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo *(Ho Lee at al 2020)*.
- A meta-analysis of 20 randomized trials (n = 8,982) assessed the efficacy of tofacitinib, baricitinib, and upadacitinib in patients with RA. Tofacitinib 10 mg (RR, 2.48; 95% CI, 1.97 to 3.14; $p < 0.001$) had to the highest ACR20 response rates followed by tofacitinib 5 mg (RR, 2.16; 95% CI, 1.81 to 2.58; $p < 0.001$). Tofacitinib displayed higher ACR 20 response rates compared with baricitinib and upadacitinib (*Wang et al 2020*).
- Another recent Cochrane review (*Hazelwood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- A network meta-analysis of individual patient data from 38 randomized controlled trials compared various MTX-biologic combinations for RA in patients with an inadequate response to MTX alone (*Janke et al 2020*). Anakinra plus MTX showed relatively less benefit than other combinations in terms of clinical remission or low disease activity, and certolizumab plus MTX showed relatively higher rates of serious adverse events or infections; however, differences between combinations were generally minor.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared

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to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).

- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; $p < 0.05$) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; $p < 0.001$). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness that is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients ($p < 0.001$) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group ($p < 0.001$) (*van der Heijde et al 2006*).
- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo ($p < 0.001$) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo ($p < 0.001$) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache, and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 ($p < 0.0001$). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group ($p < 0.0001$ for both) (*Braun et al 2011*).
- The FDA approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of

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AS demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.

- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There were significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks ($p < 0.0001$) (*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group ($p < 0.001$) (*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
  - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis, which includes AS (*Sieper et al 2015b*).
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*). Four-year results from MEASURE-1 demonstrated sustained efficacy with ASAS 20/40 response rates of 79.7%/60.8% and 71%/43.5% with secukinumab 150 mg and 75 mg, respectively, at week 208 (*Braun et al 2018*).
- The efficacy and safety of Taltz (ixekizumab) were evaluated in the Phase 3 randomized, double-blind, placebo-controlled COAST-V and COAST-W trials. In total, 657 patients were studied in these trials, including biologic DMARD-naïve patients in COAST-V and patients with previous inadequate response or intolerance to TNF inhibitors in COAST-W. The primary endpoint in both trials, ASAS 40 response at week 16, was significantly improved with ixekizumab every 4 weeks vs placebo (48% vs 18% in COAST-V, $p < 0.0001$; 25% vs 13% in COAST-W, $p < 0.017$). Common adverse events included nasopharyngitis, upper respiratory tract infection, neutropenia, and infection *(van der Heijde et al 2018[a]; Deodhar et al 2019[a])*. The ASAS 40 response seen at week 16 was sustained through week 52 in both trials and through 3 years in 1 trial (*Dougados et al 2020, van der Heijde et al 2022[a]*).
- Efficacy and safety of Xeljanz (tofacitinib) in AS were assessed in a placebo-controlled, randomized, double-blind trial in 269 patients with active disease *(Deodhar et al 2021)*. Patients were randomized to double-blind tofacitinib 5 mg twice daily or placebo for 16 weeks, followed by an additional 32 weeks of treatment with tofacitinib 5 mg twice daily in all patients. The primary endpoint of ASAS 20 response at week 16 was significantly improved in patients treated with tofacitinib compared with placebo (56% vs 29%, respectively; $p < 0.0001$).

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- Efficacy and safety of Rinvoq (upadacitinib) in AS were assessed in 2 randomized controlled trials, SELECT-AXIS 1 and SELECT-AXIS 2 (*van der Heijde et al 2019[b]; van der Heijde et al 2022[b]*). SELECT-AXIS 1 randomized 187 biologic-naïve patients with active AS to receive upadacitinib 15 mg daily or placebo and found that more patients in the upadacitinib group achieved an ASAS 40 response at week 14 (52% vs 26%; p = 0.0003) (*van der Heijde et al 2019[b]*). Clinical response was maintained for up to 2 years in the open label extension phase of SELECT-AXIS 1 (*van der Heijde et al 2022[c]*). SELECT-AXIS 2 randomized 420 patients with active AS and inadequate response to biologic DMARDs to receive upadacitinib 15 mg daily or placebo and found that more patients in the upadacitinib group achieved an ASAS 40 response at week 14 (45% vs 18%; p < 0.0001) (*van der Heijde et al 2022[b]*).
- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.
- A Bayesian network meta-analysis of 6 randomized controlled trials compared upadacitinib, secukinumab, tofacitinib, and filgotinib (not approved in the US) for the treatment of AS and found no statistically significant difference in ASAS response rates between these agents (*Lee 2022*).

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX,

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flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).

- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; CRP levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children aged 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001) (*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024). Disease control with tocilizumab was maintained at 2 years follow up with no new safety signals (*Brunner et al 2021*).
- The approval of Simponi Aria (IV golimumab) for polyarticular JIA was based on an open-label Phase 3 study (n = 127). Children 2 to < 18 years of age with active polyarticular course JIA and inadequate response to MTX were enrolled. The primary endpoints were pharmacokinetic exposure and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval at weeks 28 and 52. Other endpoints included ACR response rates. The ACR 30, 50, 70, and 90 response rates were 84%, 80%, 70%, and 47%, respectively, at week 28. Golimumab serum concentrations and AUC_{ss} were 0.40 mcg/mL and 399 mcg•day/mL at week 28. ACR response rates, serum concentrations, and AUC_{ss} were maintained at week 52 (*Ruperto et al 2021[a]*).
- The approval of Xeljanz/Xeljanz oral solution (tofacitinib) for polyarticular JIA was based on a 44-week study (n = 225) that enrolled patients 2 to 17 years old with polyarticular course JIA and inadequate responses to at least 2 DMARDs. The primary endpoint was the occurrence of disease flare at week 44. Compared with patients receiving placebo, patients receiving tofacitinib experienced significantly fewer disease flares (31% with tofacitinib vs 55% with placebo; difference in proportions -25% [95% CI, -39% to -10%]; p = 0.0007) (*Xeljanz prescribing information 2022, Ruperto et al 2021[b]*).
- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*). Patients enrolled in these trials were eligible for an open-label extension and were followed for 5 years. At 3 years, aJIA-ACR 50/70/90 response rates were 54.8%, 53.7%, and 49.7%, respectively (*Ruperto et al 2018*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the

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adalimumab group achieved the primary endpoint compared to patients in the MTX ($p < 0.001$) and placebo ($p < 0.001$) groups, respectively (*Saurat et al 2008*).

- Amjevita (adalimumab-atto) was compared with US-licensed Humira in a randomized, double-blind, multicenter study in patients with moderate to severe psoriasis and intolerance or non-response to ≥ 1 conventional systemic therapy *(Papp et al 2017[a])*. At week 16, the primary endpoint of PASI change from baseline was within the predefined equivalence margin of ± 15 (least-squares mean difference, -2.18; 95% CI, -7.39 to 3.02), demonstrating similarity of Amjevita to Humira.
  - At week 16, patients treated with Amjevita who had ≥ 50% improvement in the PASI score continued Amjevita, whereas Humira-treated patients were rerandomized to either Amjevita or Humira *(Papp et al 2017[b])*. At up to 52 weeks of treatment, patients who were rerandomized to transition from Humira to Amjevita achieved similar improvement in PASI scores as those who continued treatment with Humira.
- More than 2,200 patients were enrolled in 2 published, pivotal, Phase 3 trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 ($p < 0.0001$ for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 ($p < 0.0001$) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo ($p < 0.0001$). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).
- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; $p < 0.0001$) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; $p < 0.0001$) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
  - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on HRQoL, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (Rich et al 2016), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Otezla (apremilast) has additionally been studied in patients with moderate to severe PsO of the scalp in the Phase IIIb, double-blind, randomized, placebo-controlled STYLE trial. In this trial, 303 patients with moderate to severe scalp PsO

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who had an inadequate response to 1 or more topical scalp therapies were randomized 2:1 to receive apremilast 30 mg twice daily (with a titration period) or placebo for 16 weeks. The primary endpoint was the proportion of patients achieving ScPGA response (score of 0 or 1 with a ≥ 2-point reduction from baseline) at week 16. Patients receiving apremilast were more likely to achieve ScPGA response at week 16 (43.3% vs 13.7%; p < 0.0001) (*Van Voorhees et al 2020*).

- Otezla (apremilast) has also been studied in patients with mild to moderate PsO in a double-blind, placebo-controlled study *(Stein Gold et al 2022)*. Patients with inadequate response or intolerance to ≥ 1 topical therapy (N = 595) were randomized to apremilast 30 mg twice daily or placebo. At week 16, the primary endpoint of static Physician Global Assessment response was significantly greater with apremilast compared with placebo (21.6% vs 4.1%; p < 0.0001).
- Cosentyx (secukinumab) was evaluated in 2 large, Phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
  - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
  - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, Phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
  - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
  - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; p < 0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- Cosentyx (secukinumab) and Stelara (ustekinumab) were also compared in the 16-week randomized, double-blind CLARITY trial, which included 1102 patients with moderate to severe PsO. The co-primary endpoints were proportion of patients achieving PASI 90 response at week 12 and modified IGA score of 0/1 at week 12. Secukinumab was found be to superior to ustekinumab for both PASI 90 response (66.5% vs 47.9%; p < 0.0001) and modified IGA score of 0/1 (72.3% vs 55.3%; p < 0.0001) (*Bagel et al 2018*). The significant trend of benefit for secukinumab over ustekinumab was maintained at 52 weeks with no new safety signals (*Bagel et al 2021*).
- The efficacy of Cosentyx (secukinumab) in children 6 years of age and older with moderate to severe PsO was established in a multicenter, randomized, double-blind, active-controlled trial that enrolled 162 patients (*Bodemer et al 2021*). Patients were randomized to secukinumab low- or high-dose groups, etanercept, or placebo. In the secukinumab groups, patients with body weight < 25 kg received 75 mg (categorized as both low-dose [LD] and high-dose [HD] for this weight range), those with body weight 25 to < 50 kg received either 75 mg (LD) or 150 mg (HD), and those with body weight ≥ 50 kg received either 150 mg (LD) or 300 mg (HD). There was a significant trend of benefit in favor of LD and HD secukinumab over placebo for PASI 75 at week 12 (80.0% and 77.5%, respectively vs 14.6%; p < 0.0001 for both comparisons to placebo) and IGA score improvement to 0 or 1 (70% and 60%, respectively, vs 4.9%; p < 0.0001

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for both comparisons to placebo). Statistical significance in favor of LD and HD secukinumab was also reached for comparisons to etanercept with regard to IGA score improvement to 0 or 1 (70% and 60%, respectively vs 34.1%; $p < 0.05$) and PASI 90 (72.5% and 67.5% vs 29.3%; $p < 0.05$).

- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.
- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
  - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively ($p < 0.001$ for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively ($p < 0.001$ for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
  - UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-Q study (n = 149) evaluated the efficacy of Taltz (ixekizumab) to placebo in patients with moderate-to-severe genital psoriasis. At week 12, ixekizumab was superior to placebo for the primary endpoint of the proportion of patients achieving a score of 0 or 1 on the static PGA of genitalia (73% vs 8%, $p < 0.001$) (*Ryan et al 2018*).
- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab

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was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted p < 0.05).

- The IXORA-R study (n = 1027) compared Taltz (ixekizumab) to Tremfya (guselkumab) in adults with moderate-to-severe PsO (*Blauvelt et al 2021*). At week 24, ixekizumab was found noninferior to guselkumab for achievement of PASI 100 (50% vs 52%, respectively; difference, -2.3%; 95% CI, -8.4 to 3.8 [within the 11.4% noninferiority margin]); statistical significance was not reached for this comparison (p = 0.41).
- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
  - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).
  - AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
    - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.08 for brodalumab 140 mg vs ustekinumab). After week 52, patients receiving ustekinumab or placebo were switched to brodalumab and treatment was continued to week 120 (*Puig et al 2020*). At 120 weeks, 84.4%, 75.6%, and 61.1% of patients achieved PASI 75, PASI 90, and PASI 100, respectively, with brodalumab treatment.
    - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.007 for brodalumab 140 mg vs ustekinumab).
    - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA

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success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, NAVIGATE, and ECLIPSE trials. All were Phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p<0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs 61.7%), and week 48 (80.5% vs 55.4%; $p < 0.001$). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; $p < 0.001$). In a long-term extension of this study, PASI and IGA response rates were maintained to week 204 with continuous guselkumab treatment (*Griffiths et al 2022*).
    - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) ($p < 0.001$ for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) ($p < 0.001$). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
  - In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2018*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to blinded guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; $p < 0.001$). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; $p = 0.001$). At week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group ($p \leq 0.001$).
  - In ECLIPSE (n = 1048), patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) 100 mg SQ at weeks 0 and 4 and then every 8 weeks (n = 534) or Cosentyx (secukinumab) 300 mg SQ at weeks 0, 1, 2, 3, and 4, and then every 4 weeks (n = 514) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$). The proportion of patients with adverse events, infections, and serious adverse events were similar between the treatments.
- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, Phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1,090 patients). Enrolled adult patients with moderate-to-severe chronic PsO received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017[a]*).
  - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons).
  - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons). A higher proportion of patients in the tildrakizumab 100 mg

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group achieved PASI 75 vs etanercept (61% vs 48%, respectively; p = 0.001), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; p = 0.0663).

- The approval of Skyrizi (risankizumab-rzaa) was based on 4 randomized, double-blind, multicenter trials. In two replicate placebo- and active-controlled trials (UltIMMa-1 and -2), patients with moderate to severe chronic PsO (n = 997) assigned to risankizumab 150 mg every 12 weeks experienced significantly higher rates of PASI 90 response at week 16 (75.3% and 74.8% in UltIMMa-1 and -2, respectively) vs patients assigned to placebo (4.9% and 2.0% in UltIMMa-1 and -2, respectively) and Stelara (ustekinumab) 45 or 90 mg (42.0% and 47.5% in UltIMMa-1 and -2, respectively; p < 0.0001 for both comparisons from both trials) *(Gordon et al 2018)*. In an active controlled trial (IMMvent) in patients with moderate-to-severe chronic PsO (n = 605), PASI 90 was achieved by 72% of patients receiving risankizumab-rzaa vs 47% receiving Humira (adalimumab) (p < 0.0001) at week 16 (*Reich et al 2019[b]*). In a trial with a randomized withdrawal and retreatment design (IMMhance) (n = 507), PASI 90 was achieved by 73.2% of risankizumab-rzaa-treated patients vs 2.0% of placebo-treated patients (p < 0.001) at week 16 (*Langley et al 2019)*
- The Phase 3 IMMerge randomized noninferiority trial compared Skyrizi (risankizumab) 150 mg (n = 164) and Cosentyx (secukinumab) 300 mg (n = 163) in patients with moderate to severe PsO (*Warren et al 2021*). Risankizumab demonstrated noninferiority to secukinumab in the proportion of patients achieving PASI 90 at week 16 (73.8% vs 65.6%, respectively; difference, 8.2%; 96.25% CI, -2.2 to 18.6 [within the 12% noninferiority margin] and was superior to secukinumab at week 52 (86.6% vs 57.1%, respectively; difference, 29.8%; 95% CI, 20.8 to 38.8; p < 0.001).
- The approval of Sotyktu (deucravacitinib) was based on 2 randomized, double-blind, multicenter trials (POETYK PSO-1 and PSO-2) *(Armstrong et al 2023, Strober et al 2023)*. Adults with moderate to severe PsO who were eligible for systemic therapy or phototherapy were randomized to either deucravacitinib 6 mg once daily, placebo, or apremilast 30 mg twice daily. In both trials, deucravacitinib was superior to placebo for the co-primary endpoints of static Physician's Global Assessment (sPGA) 0/1 (PSO-1: 54% vs 7% and PSO-2: 50% vs 9%, p < 0.0001 for both) and PASI 75 (PSO-1: 58% vs 13% and PSO-2: 53% vs 9%, p < 0.0001 for both) responses at week 16. In both trials, deucravacitinib was superior to apremilast for sPGA 0/1 (PSO-1: 54% vs 32% and PSO-2: 50% vs 34%, p < 0.0001 for both) and PASI 75 (PSO-1: 58% vs 35% [p < 0.0001] and PSO-2: 53% vs 40% [p = 0.0004]) responses at week 16. In both trials, efficacy was maintained to week 52.
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) and Taltz (ixekizumab) in pediatric patients (age 6 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (p < 0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).
  - A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (p < 0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (p < 0.001 for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively (p < 0.001 for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable

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treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.
  - An open-label, single arm, multicenter, Phase 3 trial evaluated the efficacy and safety of ustekinumab in patients 6 to < 12 years of age with moderate to severe PsO (*Philipp et al 2020*). A total of 44 patients received weight-based ustekinumab at weeks 0 and 4, then every 12 weeks through week 40. At week 12, 77% of patients achieved PGA 0 or 1, 84% achieved PASI 75, and 64% achieved PASI 90. No new safety concerns were identified.
  - The IXORA-PEDS study (n = 171) evaluated the efficacy of Taltz (ixekizumab) in pediatric patients aged 6 to < 18 years with moderate to severe PsO (*Paller et al 2020*). At week 12, weight-based ixekizumab every 4 weeks was superior to placebo for the co-primary endpoints of proportion of patients achieving PASI 75 (89% vs 25%; p < 0.001) and proportion of patients achieving PGA 0 or 1 (81% vs 11%; p < 0.001). Responses were sustained through week 108 (*Paller et al 2022*).
- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (p < 0.00001) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (p < 0.00001 for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group (p < 0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥ 24 weeks) for moderate-to-severe PsO (*Nast et al 2015*). A total of 25 randomized trials (N = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 167 studies (*Sbidian et al 2022*). The network meta-analysis showed that compared to placebo, the biologics infliximab, bimekizumab (not yet approved in the US), ixekizumab, and risankizumab, were the best choices for achieving PASI 90 in patients with moderate-to-severe PsO on the basis of high-certainty evidence.
- A network meta-analysis of 41 randomized clinical trials (N = 19,248) assessed the proportion of patients with moderate-to-severe PsO who achieved PASI 100, PASI 90, and PASI 75 at weeks 10, 12, and 16 while using agents such as infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, risankizumab or guselkumab. The results revealed higher rates of PASI 100 and PASI 90 with brodalumab, ixekizumab, and risankizumab (*Tada et al 2020*).

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 (p = 0.012) in a trial (n = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (p < 0.001) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; p < 0.001) (*Mease et al 2005*).

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- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo ($p < 0.0001$). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients ($p = 0.001$). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; $p < 0.0001$). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; $p < 0.001$) (*Mease et al 2004*).
- A 24-week trial of adult patients with PsA randomized 851 patients to oral methotrexate monotherapy, etanercept monotherapy, or combination therapy. At week 24, ACR 20 response rates were significantly greater with etanercept monotherapy (60.9%) compared to methotrexate monotherapy (50.7%), but combination therapy (65%) did not provide any significant improvement over etanercept monotherapy (*Mease et al 2019*).
- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (n = 405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
  - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients ($p < 0.001$) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (n = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).
- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; $p < 0.0001$ for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response ($p < 0.001$) (*Ritchlin et al 2014*).
  - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and HRQoL were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
  - The approval of ustekinumab for PsA in patients aged 6 to 17 years was based on evidence from adequate and well-controlled studies in adults with PsO and PsA, along with pharmacokinetic data and safety data from 2 clinical

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studies in 44 patients aged 6 to 11 years with PsO and 110 patients aged 12 to 17 years with PsO (*Stelara prescribing information 2022*).

- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
  - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; $p < 0.0001$ vs placebo).
  - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
  - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
  - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively ($p < 0.0001$ for secukinumab 300 mg and 150 mg; $p < 0.05$ for 75 mg vs placebo).
  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- An additional randomized controlled trial (CHOICE) compared secukinumab at 2 doses to placebo in biologic-naïve patients with PsA and found that secukinumab 300 mg every 4 weeks was associated with a higher ACR 20 response rate than placebo at week 16 (51.5% vs 23.1%; $p = 0.001$) (*Nguyen et al 2022*). Secukinumab 150 mg every 4 weeks had a numerically higher ACR 20 response rate than placebo (36.9%) but the difference did not reach statistical significance.
- The efficacy of Otezla (apremilast) was demonstrated in 4 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a, Wells et al 2018*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b, Wells et al 2018*). In a long-term extension study, clinical improvements with Otezla were sustained up to 260 weeks (*Wells et al 2022*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017[a]*). In a Phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; $p = 0.006$) and 30/10 mg/kg (42%; $p = 0.022$) but not 3 mg/kg (33%). A Phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017[a]*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; $p < 0.001$).
- Rinvoq (upadacitinib) received FDA approval for the treatment of PsA based on the results of 2 randomized, double-blind, placebo-controlled studies in adults with moderately to severely active PsA (SELECT-PsA 1 and SELECT-PsA 2) *(McInnis et al 2021, Mease et al 2020[a])*. Patients with a previous inadequate response or intolerance to ≥ 1 non-biologic DMARD (SELECT-PsA 1) or ≥ 1 biologic DMARD (SELECT-PsA 2) were randomized to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, adalimumab (SELECT-PsA 1), or placebo as monotherapy or in combination with ≤ 2 non-biologic DMARDs for 24 weeks. The primary endpoint of both studies, ACR 20 at week 12, was significantly improved with upadacitinib 15 mg once daily (FDA-approved dose) compared with placebo in SELECT-PsA 1 (70.6% vs 36.2%; difference, 34.5%; 95% CI, 28.2 to 40.7; $p < 0.001$) and SELECT-PsA 2 (56.9% vs 24.1%; difference, 32.8%; 95% CI, 24.0 to 41.6; $p < 0.001$).
- Skyrizi (risankizumab) received FDA approval for the treatment of PsA based on the results of 2 randomized, double-blind, placebo-controlled studies, KEEPsAKE 1 and KEEPsAKE 2, in patients with active PsA (*Kristensen et al 2022*, *Östör et al 2022*). In KEEPsAKE 1, all patients had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic-naïve. In KEEPsAKE 2, patients had an inadequate response or intolerance to ≤ 2 biologic therapies and/or ≥ 1 non-biologic DMARD therapy. Risankizumab was associated with significantly higher rates of the primary endpoint of ACR 20 response at week 24 in KEEPsAKE 1 (57.3% vs 33.5%; $p < 0.001$) and KEEPsAKE 2

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(51.3% vs 26.5%; p < 0.001). Significant improvements were reported in both trials for ACR 50 and ACR 70 response at week 24. Results at 52 weeks of treatment in both KEEPsAKE 1 and KEEPsAKE 2 indicated no new safety concerns *(Kristensen et al 2022, Östör et al 2022)*.

- Taltz (ixekizumab) received FDA approval for the treatment of PsA based on 2 double-blind clinical trials, SPIRIT-P1 and SPIRIT-P2 (*Mease et al 2017[b], Nash et al 2017*). SPIRIT-P1 randomized 417 biologic naïve patients to placebo, adalimumab 40 mg every 2 weeks, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 62.1% and 57.9%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (30.2%; p ≤ 0.001). The active reference treatment, adalimumab, had an ACR 20 at week 24 of 57.4% (*Mease et al 2017[b]*). SPIRIT-P2 randomized 363 patients who had a previous inadequate response to a TNF inhibitor to placebo, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 48% and 53%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (20%; p < 0.0001) (*Nash et al 2017*).
  - An open-label extension of the SPIRIT-P1 trial followed patients through week 52, demonstrating sustained efficacy with ixekizumab. The ACR 20, ACR 50, and ACR 70 response rates for the every 4 week and every 2 weeks groups were 69.1% and 68.8%, 54.6% and 53.1%, and 39.2% and 39.6% at week 52, respectively (*van der Heijde et al 2018[b]*).
  - An additional open-label extension of the SPIRIT-P1 trial followed patients through week 156. The ACR 20, ACR 50, and ACR 70 response rate for the every 2 weeks and every 4 weeks groups were 62.5% and 69.8%, 56.1% and 51.8%, and 43.8% and 33.4%, respectively (*Chandran et al 2020*).
- SPIRIT-H2H is a 52-week multicenter, open-label study comparing ixekizumab with adalimumab in patients with PsA and without prior use of biologic DMARDs. At week 52, a higher proportion of patients treated with ixekizumab achieved the combined ACR 50 and PASI 100 response (39% vs 26%, p < 0.001) and PASI 100 response (64% vs 41%, p < 0.001) compared with the patients treated with adalimumab. Both agents yielded similar outcomes for ACR 50 (49.8% vs 49.8%, p = 0.924) (*Smolen et al 2020[b]*).
- Xeljanz (tofacitinib) received FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2017[c], Gladman et al 2017*). The OPAL Broaden trial randomized 422 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 61% in the tofacitinib 10 mg group, 33% in the placebo group (p = 0.01 vs 5 mg; p < 0.001 vs 10 mg), and 52% in the adalimumab group (*Mease et al 2017[c]*). The OPAL Beyond trial randomized 395 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 47% in the tofacitinib 10 mg group, and 24% in the placebo group (p < 0.001 for both comparisons) (*Gladman et al 2017*).
- Tremfya (guselkumab) received FDA approval for the treatment of PsA based on 2 randomized, double-blind, placebo controlled trials (*Deodhar et al 2020[c], Mease et al 2020[b]*). The DISCOVER-1 trial randomized 381 patients with active PsA despite standard therapies to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 59% and 52%, respectively, which was significantly greater than the ACR 20 response rate with placebo (22%; p < 0.0001) (*Deodhar et al 2020[c]*). The DISCOVER-2 trial randomized 741 biologic-naïve patients with PsA to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 64% and 64%, respectively, which was significantly greater than the ACR 20 response rate with placebo (33%; p < 0.0001) (*Mease et al 2020[b]*). Clinical improvements were maintained through 2 years of treatment (*McInnes et al 2022*). An additional placebo-controlled trial (COSMOS) in patients with inadequate response to TNF inhibitors found that guselkumab significantly improved ACR 20 response rates at week 24 in these patients (44.4% vs 19.8% with placebo; p < 0.001) (*Coates et al 2022[a]*).
- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in

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PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.

- The multicenter, randomized, double-blind EXCEED study compared Cosentyx (secukinumab) to Humira (adalimumab) in 853 biologic-naïve patients with active PsA and an inadequate response to DMARDs (*McInnes et al 2020*). The ACR 20 response rates at week 52 were 67% with secukinumab and 62% with adalimumab (p = 0.0719). Secukinumab did not show statistical superiority over adalimumab.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016[b]*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
  - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.
- In a network meta-analysis of 8 randomized trials (N = 3086), the efficacy and safety of apremilast were compared with tofacitinib in patients with active PsA, including treatment with tofacitinib 10 mg or 5 mg, apremilast 20 or 30 mg, and placebo *(Song et al 2019)*. Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments, followed by tofacitinib 5 mg and apremilast 20 mg. Tofacitinib 10 mg was most likely to be most effective in ACR 20 response (SUCRA = 0.785), followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), and apremilast 20 mg (SUCRA = 0.448). There were no significant differences in adverse event rates.
- A network meta-analysis of 30 randomized trials (N = 10,191) compared the efficacy of infliximab, apremilast, adalimumab, tofacitinib, ustekinumab, golimumab, abatacept, secukinumab, certolizumab, brodalumab, etanercept, and ixekizumab in PsA (*Qiu et al 2020*). Direct and indirect comparisons were performed. In direct comparisons, most

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agents were better than placebo in terms of ACR 20 response rate (except adalimumab, tofacitinib, and abatacept), and no agent was significantly different from placebo in terms of serious adverse events. In the network meta-analysis, etanercept and infliximab were more effective than golimumab for ACR 20 response, and infliximab was more effective than certolizumab for PASI 75 response. Etanercept and infliximab were ranked as the most effective treatments.

- A network meta-analysis of 30 randomized trials (only 12 randomized trials for peripheral arthritis outcome) assessed the efficacy of adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab, risankizumab, and tildrakizumab on peripheral arthritis by using ACR 70 criteria and on skin by reporting PASI 100 (*Torres et al 2021*). Secukinumab and ixekizumab had the highest probability for reaching both ACR 70 and PASI 100 responses.
- A meta-analysis of 11 randomized studies (N = 5382) revealed that TNF inhibitors, IL inhibitors, and abatacept are more likely to achieve radiographic non-progression compared with placebo (*Wu et al 2020*). Ixekizumab and adalimumab had a similar proportion of non-progressors.
- A meta-analysis of 33 trials in patients with PsA found that guselkumab was comparable to IL-17A inhibitors and TNF inhibitors for achievement of ACR20, ACR50, and ACR70 (*Mease et al 2022*). There was a trend of benefit for guselkumab vs most other active agents for achievement of PASI 90. For PASI 100, van der Heijde-Sharp score, and serious adverse events, guselkumab was comparable to other active agents.
- A network meta-analysis of 11 trials evaluated the comparative efficacy in prevention of radiographic progression PsA of biologic DMARDs, including abatacept, adalimumab, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, secukinumab, and ustekinumab *(Wang et al 2022)*. All interventions were more effective than placebo in achieving radiographic non-progression except for secukinumab 150 mg, ustekinumab, and guselkumab. SUCRA values indicated that adalimumab, certolizumab, and etanercept may be most effective in achievement of radiographic non-progression. SUCRA analysis showed that infliximab ranked the best in reducing the total radiographic score, followed by etanercept.

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
  - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥ 2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; p = 0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.
- The SYCAMORE study established the efficacy and safety of Humira (adalimumab) in pediatric patients with JIA-associated UV. The double-blind trial evaluated 90 children and adolescents ≥ 2 years of age and randomized them to adalimumab or placebo until treatment failure or 18 months had elapsed. The primary endpoint was the time to treatment failure. Sixteen treatment failures (27% of patients) occurred with adalimumab compared to 18 failures (60% of patients) with placebo (HR, 0.25; 95% CI, 0.12 to 0.90). Adverse events occurred more frequently with adalimumab (10.07 events per patient year [PY] vs 6.51 events per PY with placebo) (*Ramanan et al 2017*).

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

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Alopecia areata, Behçet disease, CAPS, CRS, DIRA, ERA, FMF, GCA, GVHD, HIDS/MKD, NOMID, NRAS, SSc-ILD, and TRAPs

- The efficacy of Otezla (apremilast) for Behçet disease was evaluated in a randomized, double-blind, placebo-controlled trial in 207 adults with Behçet disease with active oral ulcers who were previously treated with at least one nonbiologic therapy (*Hatemi et al 2019*). At week 12, apremilast 30 mg twice daily was associated with a 42.7 point mean reduction from baseline in oral ulcer pain on a visual analog scale (VAS), compared with an 18.7 point reduction with placebo. The area under the curve (AUC) of the total mean number of ulcers during the 12 week period was 129.5 in the apremilast vs 222.1 in the placebo group ; p < 0.001). The proportion of patients who were oral ulcer-free at week 12 was 53% and 22% with apremilast vs placebo, respectively. Adverse events with apremilast included diarrhea, nausea, and headache.
- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2020*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy of Kineret (anakinra) for DIRA was evaluated in a long-term natural history study of 9 patients (ages 1 months to 9 years) with genetically-confirmed DIRA who were treated with anakinra for up to 10 years. All patients achieved inflammatory remission (defined as CRP ≤ 5 mg/dL and absence of pustulosis, inflammatory bone disease, or glucocorticoid use) (*Kineret prescribing information 2020*).
- Cosentyx (secukinumab) was evaluated in a double-blind, placebo-controlled trial in 86 patients 2 to < 18 years of age with active ERA or juvenile PsA *(Cosentyx prescribing information 2021, Ruperto et al 2021[c])*. The JIA subtypes at baseline were 60.5% ERA and 39.5% juvenile PsA. Patients were treated with secukinumab during an open-label portion, followed by a randomized withdrawal phase and then open-label treatment. In patients with ERA, the primary endpoint of time to disease flare during the randomized withdrawal period demonstrated reduced risk in patients treated with secukinumab compared with placebo (hazard ratio, 0.47; 95% CI, 0.17 to 1.32).
- The efficacy of Cimzia (certolizumab) was evaluated in a Phase 3, randomized, double-blind, placebo-controlled trial in 317 patients with NRAS. Patients were randomized to certolizumab (400 mg at weeks 0, 2, and 4, followed by 200 mg every 2 weeks) or placebo in addition to nonbiologic background medication. At week 52, treatment with certolizumab was associated with a significantly higher proportion of patients achieving major improvement (≥ 2 point decrease in Ankylosing Spondylitis Disease Activity Score; 47.2% vs 7.0%; p < 0.0001) *(Deodhar et al 2019[b])*.
- The efficacy and safety of Rinvoq (upadacitinib) were evaluated in a Phase 3, randomized, double-blind, placebo-controlled trial in adults with active NRAS and inadequate response to at least 2 NSAIDs or intolerance or contraindication to NSAIDs. Patients were randomized to upadacitinib (15 mg daily; n = 156) or placebo (n = 157). At 14 weeks, the primary endpoint of ASAS 40 response was significantly improved with upadacitinib compared with placebo (44.9% vs 22.3%, respectively; difference, 22.5%; 95% CI, 12.4 to 32.5; p < 0.0001) *(Deodhar et al 2022[a])*.
- The efficacy and safety of Taltz (ixekizumab) were evaluated in NRAS in the 52 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020[a]*). In COAST-X, 303 adults with NRAS and an inadequate response or intolerance to NSAIDs were randomly assigned to ixekizumab 80 mg SQ every 4 weeks (n = 96), every 2 weeks (n = 102), or placebo (n = 105). Both primary endpoints were met with ixekizumab: ASAS 40 at week 16 (35% every 4 weeks vs 40% every 2 weeks vs 19% placebo; p = 0.0094 and p = 0.0016, respectively) and ASAS 40 at week 52 (30% every 4 weeks vs 31% every 2 weeks vs 13% placebo; p = 0.0045 and p = 0.0037, respectively). The most common treatment-emergent adverse events were nasopharyngitis and injection site reaction.
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in NRAS in the randomized, double-blind, placebo-controlled, Phase 3 PREVENT study (*Deodhar et al 2020[b]*). In this trial, 555 adults with NRAS were randomized to receive secukinumab with a loading dose, secukinumab without a loading dose, or placebo (secukinumab was dosed as 150 mg at weeks 0, 1, 2, and 3, then every 4 weeks starting at week 4). The primary analyses were performed in TNF inhibitor-naïve patients (n = 501). Both primary endpoints were met. At week 16, more patients in the secukinumab plus loading dose group achieved ASAS 40 compared with placebo (41.5% vs 29.2%; p < 0.05). At week 52, more patients in the secukinumab without loading dose group achieved ASAS 40 compared with placebo (39.8% vs 19.9%; p < 0.05).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, FMF, and adult-onset Still's disease.

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- Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (Ilaris prescribing information 2020). Published data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
- Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period (45% vs 8%, 35% vs 6%, and 61% vs 6%, respectively). Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*De Benedetti et al 2018*). In the open-label extension phase of this trial, canakinumab was effective for controlling disease activity and flares over 72 weeks; 64% of patients experienced no flares during the 72-week trial period, and 20% had 1 flare, as compared with a median of 12 flares per year reported at baseline (*Jeyaratnam et al 2022*).
- Efficacy and safety in adult-onset Still's disease were evaluated in a randomized, double-blind, placebo-controlled study of 36 patients with adult-onset Still's disease and active joint involvement. The primary endpoint, proportion of patients achieving a significant reduction in DAS28 at week 12, was achieved in 67% of canakinumab-treated patients and 41% of placebo-treated patients (p = 0.18). Proportions of patients achieving the secondary endpoints of ACR 30, 50, and 70 were significantly greater in the canakinumab group (61%, 50%, and 28% with canakinumab vs 20%, 6.7%, and 0% with placebo; p = 0.033, 0.009, and 0.049 for canakinumab vs placebo, respectively). The study was terminated prematurely due to recruitment difficulties (*Kedor et al 2020*).

- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA, CRS, and SSc-ILD.
  - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled Phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo (p < 0.01).
  - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2022*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.
  - The efficacy of tocilizumab in SSc-ILD was evaluated in a randomized, double-blind, placebo-controlled clinical trial of 210 adults with SSc-ILD (Khanna et al 2020). While this trial did not meet its primary endpoint (change from baseline to week 48 in the modified Rodnan Skin Score [mRSS], a standard outcome measure for skin fibrosis in SSc-ILD), there was a trend of benefit in favor of tocilizumab for preservation of lung function (a > 10% decrease in FVC% predicted occurred in 24% of patients in the placebo group and only 13% of patients in the tocilizumab group; HR 0.55, 95% CI, 0.3 to 1.11; p = 0.08). Treatment failure was also less likely with tocilizumab (22%) vs placebo (35%; p = 0.08). Benefits in preservation of lung function were maintained through week 96 in an open-label extension of this study (*Khanna et al 2022*).
- The efficacy and safety of Orencia (abatacept) in the prophylaxis of acute GVHD was assessed in a Phase 2 trial of adults and children with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor *(Watkins et al 2021)*. A cohort of patients with 8/8 HLA-matched HSCT (N = 142) were randomized to blinded abatacept or placebo, each in addition to a calcineurin inhibitor (CNI) and MTX. At day 100, abatacept was associated with numeric improvements in the primary endpoint of severe (grade 3 to 4) acute GVHD (hazard ratio, 0.45; 95% CI, 0.22 to 0.90). At day 180, severe acute GVHD-free-survival (SGFS) was 93.2% for CNI/MTX plus abatacept vs 82% for CNI/MTX plus placebo (p = 0.05). In an open-label single-arm cohort of patients undergoing 7/8 HLA-matched HSCT (n = 43), grade 3 to 4 acute GVHD was 2.3% for CNI/MTX plus abatacept, which compared favorably with a nonrandomized matched cohort of CNI/MTX (30.2%, p < 0.001); the SGFS was also better (97.7% vs 58.7%, p < 0.001).
  - A study using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) of patients 6 years and older who underwent HSCT from a 1 allele-mismatched unrelated donor demonstrated that treatment with

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abatacept in addition to CNI and MTX was associated with greater overall survival at day 180 post-HSCT compared with patients not treated with abatacept (98% vs 75%) (*Orencia prescribing information 2021*).

- The efficacy and safety of baricitinib for alopecia areata were assessed in 2 randomized, placebo-controlled, Phase 3 trials (BRAVE-AA1 and BRAVE-AA2) (*King et al 2022*). Both trials enrolled adults with severe alopecia areata and randomized patients to receive either baricitinib 4 mg daily, baricitinib 2 mg daily, or placebo. The primary outcome was a Severity of Alopecia Tool (SALT) score of 20 or less at week 36. In BRAVE-AA1 (N = 654), the primary outcome was achieved in 38.8%, 22.8%, and 6.2% of patients assigned to baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively ($p < 0.001$ for both doses vs placebo). In BRAVE-AA2 (N = 546), the primary outcome was achieved in 35.9%, 19.4%, and 3.3% of patients assigned to baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively ($p < 0.001$ for both doses vs placebo).
- A systematic literature review of 38 studies determined that anakinra, canakinumab, and etanercept are the most commonly studied biologics for treating familial Mediterranean fever, while studies with adalimumab, tocilizumab, rilonacept, and infliximab remain limited (*Kuemmerle-Deschner et al 2020*). The available evidence suggests that anakinra and canakinumab are effective in treating familial Mediterranean fever.

Clinical Guidelines

- RA:
  - The America College of Rheumatology (ACR) recommends the use of conventional DMARDs, a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, or rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). For patients who are not at target, switching to a medication in a different class is conditionally recommended over switching to a medication in the same class for patients receiving a biologic or JAK inhibitor. Biosimilars are considered equivalent to FDA-approved originator biologics. Anakinra was excluded from the ACR guideline because of its low use and lack of new data. (*Fraenkel et al 2021*).
  - EULAR guidelines for RA management were recently updated (*Smolen et al 2023*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD (csDMARD) strategy, in the absence of poor prognostic factors, other csDMARDs should be considered. If poor prognostic factors are present with csDMARD failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors should be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biologica or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor.
  - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2018*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
  - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
  - The ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee strongly recommends against the use of biologics (eg, TNF inhibitors, IL-1 receptor antagonists) for any form of osteoarthritis (*Kolasinski et al 2020*).
- JIA:
  - The ACR and Arthritis Foundation published a guideline for the treatment of JIA in 2019 focusing on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy (*Ringold et al 2019*).

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- A 2021 guideline from the ACR addresses the treatment of oligoarthritis, temporomandibular joint arthritis, and SJIA (*Onel et al 2022*). For SJIA, an IL-1 inhibitor or IL-6 inhibitor is conditionally recommended for initial treatment; no specific agent is preferred. Monotherapy with an NSAID may also be considered for initial treatment of SJIA without macrophage activation syndrome. Systemic glucocorticoids are conditionally recommended as part of initial therapy for patients with macrophage activation syndrome. If residual arthritis is present despite these therapies, a conventional synthetic DMARD may be added or a different biologic therapy may be tried. Patients without macrophage activation syndrome who experience incomplete response or intolerance to an initial IL-1 or IL-6 inhibitor may be switched to an alternative IL-1 or IL-6 inhibitor.

- PsO and PsA:
  - Joint guidelines from the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) state that topical medications (eg, corticosteroids, vitamin D analogues) are the most common agents used to treat mild to moderate PsO. They are commonly used as adjunctive therapy to phototherapy, systemic agents, and biologics (*Elmets et al 2021*). Phototherapy is viewed as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications (*Elmets et al 2019*). Although biologic therapies have changed the treatment landscape, non-biologic systemic agents (eg, methotrexate) either as monotherapy or in combination with biologics, are still widely used due to benefit for widespread disease, comparatively low cost, increased availability, and ease of administration (*Menter et al 2020[a]*).
  - Joint guidelines from the AAD/NPF on the treatment of psoriasis with biologics address the effectiveness of these drugs as monotherapy or in combination to treat moderate-to-severe disease in adults. The guideline does not provide relevant ranking for preferences of individual biologics, but does recommend that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can all be recommended as a monotherapy option for patients. Further recommendations on specific presentations of the disease, combination therapy, and dosing recommendations are included in the guidance (*Menter et al 2019*).
  - The AAD/NPF guideline on PsO in pediatric patients states that etanercept, adalimumab, and ustekinumab are effective biologic therapies for moderate to severe pediatric psoriasis. Infliximab can be recommended as monotherapy or in combination with MTX for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening (*Menter et al 2020[b]*).
  - EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate (*Gossec et al 2020, Kerschbaumer et al 2020*).
  - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, an IL-23 inhibitor, an IL-17 inhibitor, a JAK inhibitor, or a PDE-4 inhibitor (*Coates et al 2022[b]*).
  - The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy (MTX, sulfasalazine, leflunomide, cyclosporine, or apremilast) can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics (secukinumab, ixekizumab, brodalumab), IL-12/23 biologics (ustekinumab), abatacept, and tofacitinib (*Singh et al 2019*).
  - In 2020, the International Psoriasis Council Biosimilar Working Group published a consensus statement for the use of biosimilars in the treatment of patients with psoriasis (*Cohen et al 2020*). There was consensus from the Group that prescribing biosimilars to biologic-naïve patients or switching a stable patient from a reference product to a biosimilar product is appropriate if the patient and physician agree to do so. Furthermore, switching between different biosimilars should be performed with caution, until more evidence is generated supporting this practice, and multiple switches between various biosimilars and reference biologics is not the preferred option but is acceptable. Lastly, treatment switches should not occur in less than an adequate period of time (usually 6 months) from initiation of the reference product, allowing full assessment of its therapeutic effect.

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- AS:
  - The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network joint recommendations for treatment of AS and NRAS were updated in 2019. Patients with active AS or NRAS who do not respond to initial NSAID therapy are conditionally recommended to be treated with sulfasalazine, MTX, or tofacitinib; sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Patients who do not respond to NSAID therapy are strongly recommended to receive treatment with a TNF inhibitor, although no particular TNF inhibitor is preferred. Treatment with a TNF inhibitor is conditionally recommended over tofacitinib, secukinumab, and ixekizumab in these patients. In patients with active disease who have primary nonresponse with a TNF inhibitor, treatment with secukinumab or ixekizumab is strongly recommended, and treatment with tofacitinib is conditionally recommended. Patients with secondary nonresponse to treatment with a TNF inhibitor are conditionally recommended to receive treatment with an alternative TNF inhibitor. In patients with AS and inflammatory bowel disease or recurrent iritis, TNF inhibitors are conditionally recommended over treatment with other biologics. In patients with stable disease who are treated with an originator TNF inhibitor, the guideline strongly recommends continuing the originator TNF inhibitor over mandated switching to its biosimilar (*Ward et al 2019*).
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR and were updated in 2022. The guideline notes that radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis are part of the same disease spectrum, and therefore uses the term axial spondyloarthritis in recommendations. The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered, but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. TNF inhibitors, IL-17A inhibitors, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with a TNF inhibitor or IL-17A inhibitor. In patients with a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNF. In patients with significant psoriasis, an IL-17 inhibitor may be preferred. Following failure of the first biologic or targeted synthetic DMARD, switching to another biologic DMARD (TNF inhibitor or IL-17A inhibitor) or a JAK inhibitor should be considered. For patients in sustained remission, tapering of a biologic DMARD can be considered (*Ramiro et al 2023*).
- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
  - A 2019 guideline by the ACR and Arthritis foundation focusing on children with JIA-associated UV conditionally recommended starting a monoclonal antibody TNF inhibitor over etanercept in children and adolescents with chronic anterior UV. Children and adolescents with inadequate response to one monoclonal TNF inhibitor are conditionally recommended to be treated with an escalated dose and/or frequency of the TNF inhibitor over switching to another TNF inhibitor; patients failing dose escalation are conditionally recommended to switch to another monoclonal TNF inhibitor. Children and adolescents failing MTX and 2 monoclonal TNF inhibitors are conditionally recommended to receive abatacept or tocilizumab as biologic DMARD options (*Angeles-Han et al 2019*).
- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
  - For the management of HS, the US and Canadian Hidradenitis Suppurativa Foundation recommend adalimumab to improve disease severity and QoL in patients with moderate-to-severe disease (*Alikhan et al 2019*). Additionally,

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infliximab is recommended for moderate-to-severe disease; however, the optimal dose is not currently known. Anakinra and ustekinumab may be effective agents for HS as well.
- For the management of GCA, EULAR recommendations state that tocilizumab (or methotrexate as an alternative) should be used as an adjunctive therapy in patients who have refractory or relapsing disease or who are at an increased risk of glucocorticoid-related adverse effects or complications (*Hellmich et al 2020*). A joint guideline from the ACR and Vasculitis Foundation recommends the use of oral or IV glucocorticoids, tocilizumab, and other non-glucocorticoid immunosuppressive drugs (eg, methotrexate, abatacept); specific recommendations depend on various factors such as the patient's clinical presentation, comorbidities, and prior therapies (*Maz et al 2021*).
- A EULAR guideline states that cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with progressive disease (*Kowal-Bielecka et al 2017*).
- In children and adolescents with JIA and active enthesitis, ACR guidelines conditionally recommend TNF inhibitor therapy over methotrexate or sulfasalazine (*Ringold et al 2019*).
- A EULAR guideline for the management of IL-1-mediated autoinflammatory disorders provides recommendations for the management of CAPS, TRAPS, MKD, and DIRA (*Romano et al 2022*). The guideline states that IL-1 inhibitor therapy has become the preferred treatment for these disease states; a therapeutic trial with an IL-1 inhibitor may be started when strong clinical suspicion of CAPS, TRAPS, MKD, or DIRA exists. For CAPS, IL-1 inhibitors (anakinra, canakinumab, and rilonacept) are considered standard of care; anakinra may be the most effective treatment for CNS disease. For TRAPS, IL-1 inhibitors are more effective than traditional DMARDs or other biologic DMARDs. For MKD, IL-1 inhibitors are first-line; if these therapies are not effective or available, TNF inhibitors may be considered. For DIRA, anakinra and rilonacept are recommended.
- No recent guidelines were identified for alopecia areata, CRS, or Still's disease.

Safety Summary

- Contraindications:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Cimzia (certolizumab), Cosentyx (secukinumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Skyrizi (risankizumab), Stelara (ustekinumab), and Taltz (ixekizumab) in patients with hypersensitivity to any component of the product.
  - Enbrel (etanercept) in patients with sepsis.
  - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR/Xeljanz oral solution (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
  - In addition, Avsola (infliximab-axxq), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib) have warnings for increased risk of thrombosis and death, including sudden cardiovascular death. Rinvoq (upadacitinib) and Olumiant (baricitinib), other JAK inhibitors, also carry a boxed warning for this risk.
    - In September 2021, the FDA announced that its review of a large randomized safety clinical trial comparing Xeljanz (tofacitinib) vs a TNF inhibitor in RA found an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with tofacitinib. The final results showed an increased risk of adverse events with the lower dose as well as the higher dose. The FDA believes that baricitinib and upadacitinib have similar risks because they share the same mechanism of action. The FDA has limited all approved uses of baricitinib, tofacitinib, and upadacitinib to certain patients who have not responded or cannot tolerate 1 or more TNF inhibitors.

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- Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
- Siliq (brodalumab) has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
- Olumiant (baricitinib) has a boxed warning for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.

- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Cytopenias and pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Malignancy and lymphoproliferative disorders
  - Avoiding live vaccinations and therapeutic infectious agents
  - Noninfectious pneumonia with Stelara (ustekinumab)
  - Increased lipid parameters and liver function tests with Actemra (tocilizumab), Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib) and Kevzara (sarilumab)
  - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Depression with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs)
  - Thrombosis with Olumiant (baricitinib)
  - Embryo-fetal toxicity with Rinvoq (upadacitinib)
  - Hepatotoxicity with Actemra (tocilizumab)
  - Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
  - Macrophage activation syndrome with Ilaris (canakinumab)
  - Posterior reversible encephalopathy syndrome (PRES) with Stelara (ustekinumab)
  - Consult prescribing information for other drug-specific warnings/precautions
  - Cytomegalovirus and Epstein-Barr Virus reactivation (abatacept)
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension, and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 PY and 2.8 events per 100 PY, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 PY), and upper respiratory infections (rate of 7.3 per 100 PY). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 PY for malignancies.

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- Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 PY), malignancies (3.2 events per 100 PY), and autoimmune events (1.2 events per 100 PY). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.
- A randomized controlled noninferiority trial compared tofacitinib to TNF inhibitors in terms of risk for major cardiovascular adverse events and malignancy (*Ytterberg et al 2022*). A total of 1455 patients with active RA and at least 1 additional cardiovascular risk factor were randomized to receive tofacinitib 5 or 10 mg twice daily or a TNF inhibitor. During a median follow-up of 4 years, major cardiovascular adverse events were more common among patients receiving tofacitinib (3.4% vs 2.5%; hazard ratio, 1.33; 95% CI, 0.91 to 1.94), as were malignancies (4.2% vs 2.9%; hazard ratio, 1.48; 95% CI, 1.04 to 2.09). Noninferiority was not established for tofacitinib vs TNF inhibitors for either endpoint.
- Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 PY. The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
- A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.
- A systematic review and network meta-analysis analyzed 42 randomized controlled trials and found no significant difference between the available JAK inhibitors in terms of major adverse cardiovascular events or venous thromboembolic events (*Alves et al 2022*).
- A pooled analysis of 9 RA trials evaluating baricitinib included 3492 patients (7860 PY exposure). The incidence rate for major adverse cardiovascular events was comparable between placebo (0.5 per 100 PY) and baricitinib 4 mg (0.8 per 100 PY). Incidence rates for arterial thrombotic events and congestive heart failure were also similar between baricitinib and placebo. The occurrence of a deep vein thrombosis or pulmonary embolism occurred more frequently in the baricinitib 4 mg group (6 events in 997 patients) vs placebo (0 events in 1070 patients) (*Taylor et al 2019*). Another pooled analysis of 10 RA trials including 3770 patients (14,744 patient-years exposure) examined the safety of baricitinib over a median of 4.6 years and a maximum of 9.3 years. In this analysis, the incidence rates for serious infections, herpes zoster, major cardiovascular adverse events, malignancy, and deep vein thrombosis/pulmonary embolism were 2.6, 3.0, 0.5, 1.0, and 0.5 per 100 patient-years, respectively (*Taylor et al 2022*).

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- PsO
  - A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
  - In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
  - In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
  - In a 5-year extension study, 1349 patients treated with guselkumab in VOYAGE 1 and VOYAGE 2 were evaluated for long-term safety; during 7166 patient-years of follow-up, the incidence rates for serious infections, nonmelanoma skin cancer, malignancy other than nonmelanoma skin cancer, and major adverse cardiovascular events were 0.85, 0.34, 0.45, and 0.29 per 100 patient-years, respectively (*Blauvelt et al 2022*).
  - A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.
- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
  - An integrated safety analysis of 4 clinical trials examined the safety of ixekizumab in 1401 patients with PsA (2247.7 patient-years of exposure) (*Deodhar et al 2022[b]*). In this study, the exposure-adjusted incidence rates of serious infections, malignancies, inflammatory bowel disease, depression, and major cerebrocardiovascular events were 1.2, 0.7, 0.1, 1.6, and 0.5 per 100 PY, respectively. No new safety signals were observed.
- AS
  - A meta-analysis of 25 randomized controlled studies with 2403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).

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- Another meta-analysis of 14 randomized controlled trials with 2032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).

- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
  - Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
  - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
  - The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 PYs. Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular adverse events (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
  - Several meta-analyses evaluated the safety of TNF inhibitors.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
  - For Olumiant (baricitinib), adjust dose when used with potent inhibitors of organic anion transporter (OAT) 3.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.

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- Patients must enroll in the program.
- Pharmacies must be certified with the program and must only dispense to patients who are enrolled in the program.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: < 100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; ≥ 100 kg, 162 mg administered SQ every week. **PJIA:** IV: < 30 kg, 10 mg/kg IV every 4 weeks; ≥ 30 kg, 8 mg/kg IV every 4 weeks. SQ: < 30 kg, 162 mg SQ every 3 weeks; ≥ 30 kg, 162 mg SQ every 2 weeks. **SJIA:** IV: < 30 kg, 12 mg/kg IV every 2 weeks; ≥ 30 kg, 8 mg/kg IV every 2 weeks SQ: < 30 kg, 162 mg SQ every 2 weeks; ≥ 30 kg, 162 mg SQ once weekly. **GCA:** IV: 6 mg/kg IV every 4 weeks with tapering glucocorticoids. SQ: 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** < 30 kg, 12 mg/kg IV; ≥ 30 kg, 8	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, SSc-ILD, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count, infection, and low ANC. **PJIA**: Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.	Give as a single 60-minute intravenous infusion. < 30 kg, use a 50 mL infusion bag. ≥ 30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites. SQ administration with the prefilled autoinjector has not been studied in SSc-ILD. IV administration is not approved for SSc-ILD. Laboratory abnormalities in patients with GCA may warrant dose interruption with IV administration and dose interruption or reduction with SQ administration. Doses > 600 mg per infusion not recommended in GCA.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		mg/kg IV; maximum, 800 mg per infusion. **SSc-ILD:** 162 mg SQ once weekly		
Amjevita (adalimumab-atto)	Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Prefilled autoinjector: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA:** 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week **PsO:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose.	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.
Avsola (infliximab-axxq)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen, and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		PsO: 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4, followed by 200 mg every other week (for body weight ≤ 90 kg) **AS, NRAS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.		
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL, 75 mg/0.5 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks; for some patients, 150 mg may be acceptable. **PsO in pediatric patients ≥ 6 years of age:** Dose is based on weight (< 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed every 4 weeks. **PsA, AS, NRAS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks. **PsA in pediatric patients:** Dose is based on weight (≥ 15 kg and < 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed by every 4 weeks. **ERA:** Dose is based on weight (≥ 15 kg and < 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4,	**PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA or AS continues in adults, consider 300 mg dose every 4 weeks.	Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		followed by every 4 weeks.		
Enbrel (etanercept)	Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL Prefilled SureClick autoinjector: 50 mg/mL Multiple-use vial: 25 mg lyophilized powder Solution: 50 mg/mL in Enbrel Mini® cartridge for use with reusable autoinjector only Single-dose vial: 25 mg/0.5 mL	**RA, AS, PsA:** 50 mg SQ weekly. **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly. **PJIA and PsO (pediatrics):** ≥ 63 kg, 50 mg SQ weekly; < 63 kg, 0.8 mg/kg SQ weekly.	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued. **JIA:** NSAIDs glucocorticoids, or analgesics may be continued.	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to < 15 kg: 10 mg SQ every other week; 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week **HS:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **HS in adolescent patients ≥ 12 years and older:** 30 kg to < 60 kg: 80 mg on day 1, 40 mg on day 8;	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		maintenance dose is 40 mg every other week. ≥ 60 kg: 160 mg on day 1, 80 mg on day 15, 40 mg on day 29; maintenance dose is 40 mg every week.		
Ilaris (canakinumab)	Single-dose vial: 150 mg injection solution	**SJIA and adult-onset Still's disease:** ≥ 7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥ 15 to ≤ 40 kg, 2 mg/kg SQ; > 40 kg, 150 mg SQ; frequency every 8 weeks. **TRAPS, HIDS/MKD, and FMF**: ≤ 40 kg, 2 mg/kg SQ; > 40 kg, 150 mg SQ; frequency every 4 weeks.	**For CAPS:** children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg. **For TRAPS, HIDS/MKD, and FMF:** If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤ 40 kg) or 300 mg (weight > 40 kg).	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks.		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		maintenance regimen of 5 mg/kg every 6 weeks.		
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID) and DIRA:** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily. CrCl < 30 mL/min: give dose every other day	Patients may be taught to self-inject. A new syringe must be used for each dose.
Olumiant (baricitinib)	Tablet: 1 mg, 2 mg, and 4 mg	**RA:** 2 mg once daily. **Alopecia areata:** 2 mg once daily; increase to 4 mg once daily if response is inadequate	**Alopecia areata**: for patients with nearly complete or complete scalp hair loss, consider treating with 4 mg once daily; once patients achieve an adequate response to treatment with 4 mg, decrease the dosage to 2 mg daily Dosage modification may be required for cytopenias or anemia, or when used concomitantly with potent OAT3 inhibitors. Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine.	May be taken with or without food. Tablets may be crushed and dispersed in water for patients unable to swallow whole tablets.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Renal: Use not recommended in patients with estimated glomerular filtration rate < 30 mL/min/1.73m^2; adjust dosage in patients with estimated glomerular filtration rate between 30 and 60 mL/min/1.73 m^2.	
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: < 60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; > 100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and < 75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. > 75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to < 25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule.	Before administering for treatment of GVHD, administer recommended antiviral prophylaxis.	IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		SQ: 125 mg once weekly without IV dose. **GVHD:** IV: ≥ 6 years: 10 mg/kg (maximum 1000 mg) on the day before transplantation, then administration on days 5, 14, and 28 after transplantation. ≥ 2 to < 6 years: 15 mg/kg (maximum 1000 mg) on the day before transplantation, then 12 mg/kg on days 5, 14, and 28 after transplantation.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO, Behçet's:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily.	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Infuse over 2 hours. Do not administer with other drugs.
Renflexis (infliximab-abda)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Riabni (rituximab-arrx)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Rinvoq (upadacitinib)	Extended release tablet: 15 mg, 30 mg, and 45 mg	**RA, PsA, AS, NRAS:** 15 mg once daily.		May be administered with or without food.
Rituxan (rituximab)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		no sooner than every 16 weeks.		
Ruxience (rituximab-pvvr)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks.	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation.	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/Simponi Aria (golimumab)	SmartJect autoinjector: 50 mg/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL Aria, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks. **Aria (PJIA):** 80 mg/m^2 IV at weeks 0 and 4, and then every 8 weeks.	**RA:** give with MTX. **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Skyrizi (risankizumab-rzaa)	Prefilled syringe: 75 mg/0.83 mL, 150 mg/mL	**PsO, PsA:** 150 mg SQ at week 0, week 4, and every 12 weeks thereafter.	Product is not made with natural rubber latex.	Each dose must be administered in different anatomic locations.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Prefilled pen (autoinjector): 150 mg/mL Prefilled cartridge with on-body injector (for CD only): 360 mg/2.4 mL Vial (for IV infusion in CD only): 600 mg/10 mL		**PsA**: give with or without non-biologic DMARD.	Patients may be taught to self-inject using the prefilled syringes or pen.
Sotyktu (deucravacitinib)	Tablet: 6 mg	**PsO:** 6 mg once daily	Not recommended in severe hepatic impairment.	May take with or without food.
Stelara (ustekinumab)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose	**Co-existent moderate-to-severe PsO with PsA weighing >100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that Stelara be administered by a healthcare provider. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		initially, 4 weeks later, then every 12 weeks.		
Taltz (ixekizumab)	Prefilled syringe: 80 mg/mL Autoinjector: 80 mg/mL	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. **PsO (6 to < 18 years old):** < 25 kg, 40 mg SQ at week 0 then 20 mg every 4 weeks; 25 to 50 kg, 80 mg SQ at week 0 then 40 mg every 4 weeks; > 50 kg, 160 mg SQ at week 0, then 80 mg every 4 weeks. **PsA, AS:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks. **NRAS:** 80 mg by SQ injection every 4 weeks. NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		Patients weighing >50 kg may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites. Doses for patients weighing ≤50 kg must be administered by a healthcare professional. Contents of a prefilled syringe should be transferred to a sterile vial, and the appropriate dose drawn out of the vial into a new syringe.
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled autoinjector: 100 mg/mL	**PsO, PsA:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks	For **PsA**, Tremfya may be used alone or in combination with MTX.	Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Truxima (rituximab-abbs)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Xeljanz/Xeljanz XR (tofacitiib)	Tablet: 5 mg, 10 mg Extended-release Tablet: 11 mg, 22 mg Oral solution: 1 mg/mL	**RA, AS:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily or 11 mg once daily used in combination with nonbiologic DMARDs **PJIA:** 3.2 mg (3.2 mL oral solution) twice daily if weight ≥ 10 kg but < 20 kg; 4 mg (4 mL oral solution) twice daily if weight ≥ 20 kg but < 40 kg; and 5 mg (tablet or 5 mL oral solution) twice daily if weight ≥ 40 kg.	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Xeljanz XR is not interchangeable or substitutable with Xeljanz oral solution. Dose adjustment needed in patients taking CYP450 inhibitors, and with moderate or severe renal impairment, moderate hepatic impairment, lymphopenia, neutropenia, and anemia. Moderate to severe impairment: Patients with RA, PsA, or AS receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. For patients on hemodialysis, administer doses after the dialysis session. Do not take supplemental doses if a dose was taken before dialysis.	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew. Xeljanz should not be initiated in patients with absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, or hemoglobin < 9 g/dL. Administer Xeljanz oral solution with the included press-in bottle adapter and oral dosing syringe.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Hepatic impairment: Patients with RA, PsA, or AS receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. Not recommended in severe hepatic impairment.	

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DIRA=deficiency of interleukin-1 receptor antagonist; DMARD=disease-modifying anti-rheumatic drug; ERA=enthesitis-related arthritis; GCA=giant cell arteritis; GVHD: graft-vs-host disease; HS=hidradenitis suppurative; IV=intravenous infusion; JAK=Janus kinase; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NRAS=nonradiographic axial spondyloarthritis; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; SSc-ILD=systemic sclerosis-associated interstitial lung disease.
See the current prescribing information for full details.

Conclusion

- Immunomodulators are available for a variety of conditions associated with inflammation. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
  - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
  - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
  - In patients with RA, upadacitinib was superior to abatacept for changes in the DAS28-CRP and the achievement of remission (*Rubbert-Roth et al 2020*).
  - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
  - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
  - In patients with RA and inadequate response or intolerance to MTX, upadacitinib was associated with significantly greater ACR 20 response compared with adalimumab at weeks 12 and 26 *(Fleischman et al 2018).*
  - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have noninferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).

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- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
- Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR and CLARITY studies, which were double-blind, randomized controlled trials in 676 and 1102 patients, respectively, with moderate to severe PsO (*Bagel et al 2018, Thaçi et al 2015*). In both studies, the proportion of patients achieving PASI 90 was significantly higher with secukinumab compared to ustekinumab (CLEAR: 79% vs 57.6%, $p < 0.0001$; CLARITY: 66.5% vs 47.9%, $p < 0.0001$) at week 16 in CLEAR and at week 12 in CLARITY.
- In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; $p < 0.001$) (*Reich et al 2017[b]).*
- In the IXORA-R study, ixekizumab was found noninferior to guselkumab for achievement of PASI 100 at week 24 (50% vs 52%, respectively; statistical significance was not reached for this comparison ($p = 0.41$) (*Blauvelt et al 2021).*
- A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
- In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
- In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
- In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
- In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
- In two trials of patients with moderate to severe chronic PsO, risankizumab was associated with significant improvement in PASI 90 response at week 16 vs ustekinumab *(Gordon et al 2018)*.
- In the IMMerge trial, risankizumab was noninferior to secukinumab for the proportion of patients achieving PASI 90 at week 16 (73.8% vs 65.6%, respectively) and was superior to secukinumab at week 52 (86.6% vs 57.1%, respectively; $p < 0.001$) (*Warren et al 2021*).
- In ECLIPSE, patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) or Cosentyx (secukinumab) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$).
- No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
- In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
- In the SPIRIT-H2H study, ixekizumab led to a higher proportion of patients with PsA achieving the combined ACR 50 and PASI 100 and PASI 100 alone compared with adalimumab (*Smolen et al 2020[b]*)
- More comparative studies are needed.

- For RA, the ACR recommends the use of conventional DMARDs, a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, or rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). Biosimilars are considered equivalent to FDA-approved originator biologics (*Fraenkel et al 2021*). EULAR guidelines for RA management were recently updated (*Smolen et al 2023*). EULAR recommends that therapy with DMARDs should be

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initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors must be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor. EULAR has also released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).

- EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2020, Kerschbaumer et al 2020*). For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate.
- Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, JAK inhibitors, and PDE-4 inhibitors (*Coates et al 2022[b]*). Joint guidelines from the AAD/NPF on the treatment of PsO with biologics do not provide ranking for preferences of individual biologics, but do note that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can be recommended as a monotherapy option for patients with moderate to severe PsO (*Menter et al 2019*).
- The ACR/NPF guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics, IL-12/23 biologics, abatacept, and tofacitinib (*Singh et al 2019*).
- The ACR guideline for SJIA conditionally recommends an IL-1 inhibitor or IL-6 inhibitor for initial treatment; no specific agent is preferred (*Onel et al 2022*). Patients with JIA and active sacroiliitis or enthesitis are recommended to receive TNF inhibitor therapy, and patients with non-systemic polyarthritis are recommended to receive TNF inhibitor therapy, abatacept, or tocilizumab. Patients with continued disease activity and primary TNF inhibitor failure are recommended to receive abatacept or tocilizumab *(Ringold et al 2019)*.
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that TNF inhibitors, IL-17A inhibitors, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with a TNF inhibitor or IL-17A inhibitor (*Ramiro et al 2023*). The 2019 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients. Secukinumab or ixekizumab are recommended in patients with active disease who have primary nonresponse with a TNF inhibitor (*Ward et al 2019*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, tofacitinib, sarilumab, baricitinib, and upadacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors, tofacitinib, baricitinib, and upadacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior. Tofacitinib (10 mg twice daily dose), upadacitinib, and baricitinib also have boxed warnings regarding thrombosis risk.
  - A final FDA review of a large randomized safety clinical trial comparing Xeljanz (tofacitinib) vs a TNF inhibitor found an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with tofacitinib. The final results showed an increased risk of adverse events with the lower dose as well as the higher

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dose. The FDA believes that baricitinib and upadacitinib have similar risks because they share the same mechanism of action. The FDA required revisions to the Boxed warning, several sections of the prescribing information, and the patient medication guide and limited all approved uses to certain patients who have not responded or cannot tolerate 1 or more TNF inhibitors for tofacitinib and, because they share the same mechanism of action, baricitinib and upadacitinib (*FDA Drug Safety Communication 2021*).

- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast, baricitinib, tofacitinib, and upadacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast, baricitinib, tofacitinib, and upadacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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