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REVIEW ARTICLE

Use of IL-23 Inhibitors for the Treatment of Plaque Psoriasis and Psoriatic Arthritis: A Comprehensive Review

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Abstract

Psoriasis is a common inflammatory skin disease with multiple comorbidities, including psoriatic arthritis and coronary artery disease, that can severely impact an individual's quality of life and daily functioning. In recent years, enhanced understanding of the pathogenesis of psoriasis, especially the role of T helper 17 cells, has resulted in the development of new classes of biologic drugs targeting modulators along its disease pathway. Among these, inhibitors of interleukin-23 (e.g., ustekinumab, guselkumab, tildrakizumab, and risankizumab) have emerged as safe and effective options for the treatment of moderate-to-severe plaque psoriasis; ustekinumab and guselkumab have additionally been approved to treat psoriatic arthritis. Selective interleukin-23 inhibitors require less frequent dosing than interleukin-17 inhibitors and may possess a more favorable risk profile without an increased risk of candidiasis or inflammatory bowel disease. Overall, these highly effective medications are contributing to a rising standard for psoriasis outcomes through resolution of skin lesions and joint manifestations and improvement of patient quality of life.

Key Points

Interleukin (IL)-23 plays an important role in the development of psoriasis and psoriatic arthritis.

IL-23 inhibitors are effective in treating psoriasis and psoriatic arthritis.

IL-23 inhibitors are safe and do not show a significantly increased risk for adverse events.

1 Introduction

Psoriasis is a chronic inflammatory disease affecting over 7 million people in the USA with an estimated annual financial burden of over US$112 billion [1, 2]. Plaque psoriasis is the most common subtype and classically manifests as erythematous plaques with an overlying micaceous silvery scale on the trunk and extensor surfaces of the extremities; less common subtypes include inverse, guttate, and pustular [3, 4]. Nail lesions, such as pitting and onycholysis, may also be seen. Psoriasis is also associated with multiple comorbidities, including cardiovascular disease, metabolic syndrome, psychiatric conditions, malignancy, renal disease, and hepatic disease [5].

Psoriatic arthritis (PsA) is an inflammatory arthritis that may co-occur in up to a third of patients with psoriasis [6]. Psoriatic arthritis clinically presents with dactylitis, as well as enthesitis of the plantar fascia and Achilles tendon [7]. Psoriatic arthritis usually arises approximately 10 years after the onset of psoriatic lesions. However, it may precede the skin findings in 15% of cases [7]. Psoriatic arthritis may be difficult to distinguish from other inflammatory arthritides, but the morbidity of the disease warrants a low threshold for initiation of therapy.

The pathogenesis of psoriasis stems from dysregulation of the immune system, resulting in chronic inflammation and uncontrolled keratinocyte proliferation. Early studies demonstrated the presence and potential interaction of dendritic cells and T lymphocytes in psoriatic lesions [8, 9]. Originally, T helper 1 cells, activated by dendritic cell-produced interleukin (IL)-12, were implicated in psoriasis via production of tumor necrosis factor-α (TNF-α) and interferon-γ;

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however, these cytokines showed no involvement in regulating keratinocyte proliferation [10–12]. Subsequently, the subset of T helper cells known as T helper 17 (Th17) cells and its production of IL-17 and IL-22 were identified to be central in driving psoriasis [13–17]. In particular, keratinocytes are stimulated to increase chemokine expression that perpetuates recruitment of Th17 cells [18, 19]. Upstream of this key component, dendritic cells produce IL-23 to promote differentiation and proliferation of the Th17 cells [20, 21]. Interestingly, a novel study reporting single-cell RNA sequencing of psoriatic human epidermis identified elevated populations of proliferative and ion channel genes. In addition, psoriatic epidermis was also found to be enriched for $CD1C^{+}CD301A^{+}$ myeloid dendritic cells [22]. Similarly, Th17 cells have been heavily associated with the pathogenesis of PsA [23, 24]. While incompletely understood, PsA is generally thought to result from migration of dendritic cells out of the skin into the joint space, resulting in chronic inflammation in the synovial fluid [25, 26]. Further, IL-22 plays a role in upregulating RANKL to induce osteoclast formation, bone erosion, and new bone formation [27, 28].

Treatment of psoriasis has traditionally focused on suppressing the immune system and keratinocyte proliferation, such as with methotrexate, cyclosporine, and acitretin. With elucidation of the immunological processes underlying psoriasis, biologic drugs have rapidly come to the forefront for targeting of modulators along these pathways, including TNF-α, IL-17, and IL-23. In the last 5 years, seven biologic drugs have been approved by the US Food and Drug Administration (FDA) to treat plaque psoriasis (Table 1). Ustekinumab, approved by the FDA in 2009, targets the p40 subunit shared by IL-23 and IL-12. We include ustekinumab in this review because it is partially an IL-23 inhibitor.

Guselkumab, tildrakizumab, and risankizumab have been approved in the last 3 years with targeting of the p19 subunit of IL-23 (Table 2). At the time of this writing, mirikizumab remains under development. This review evaluates the efficacy and safety of IL-23 inhibitors in the treatment of plaque psoriasis and psoriatic arthritis.

Table 1 US Food and Drug Administration (FDA)-approved biologic drugs

Drug	Mechanism	Route of administration	Year of FDA approval
FDA-approved biologic drugs for plaque psoriasis			
Risankizumab	Humanized IgG1 monoclonal antibody binding p19 subunit of IL-23	Subcutaneous	2019
Certolizumab	Humanized PEGylated Fab fragment binding TNF-α	Subcutaneous	2018
Tildrakizumab	Humanized IgG1κ monoclonal antibody binding p19 subunit of IL-23	Subcutaneous	2018
Guselkumab	Human IgG1λ monoclonal antibody binding p19 subunit of IL-23	Subcutaneous	2017
Brodalumab	Human monoclonal IgG2 antibody binding IL-17RA	Subcutaneous	2017
Ixekizumab	Humanized IgG4 monoclonal antibody binding IL-17A	Subcutaneous	2016
Secukinumab	Human IgG1 monoclonal antibody binding IL-17A	Subcutaneous	2015
Ustekinumab	Human IgG1κ monoclonal antibody binding shared p40 subunit of IL-12 and IL-23	Subcutaneous	2009
Adalimumab	Human IgG1 monoclonal antibody binding TNF-α	Subcutaneous	2008
Infliximab	Chimeric IgG1κ monoclonal antibody binding TNF-α	Intravenous	2006
Etanercept	Decoy TNF receptor	Subcutaneous	2004
FDA-approved biologic drugs for psoriatic arthritis			
Guselkumab	Human IgG1λ monoclonal antibody binding p19 subunit of IL-23	Subcutaneous	2020
Ixekizumab	Humanized IgG4 monoclonal antibody binding IL-17A	Subcutaneous	2017
Abatacept	Binds CD80 and CD86	Intravenous/subcutaneous	2017
Secukinumab	Human IgG1 monoclonal antibody binding IL-17A	Subcutaneous	2016
Certolizumab	Humanized PEGylated Fab fragment binding TNF-α	Subcutaneous	2013
Ustekinumab	Human IgG1κ monoclonal antibody binding shared p40 subunit of IL-12 and IL-23	Subcutaneous	2013
Golimumab	Human IgG1κ monoclonal antibody binding TNF-α	Subcutaneous	2009
Adalimumab	Human IgG1 monoclonal antibody binding TNF-α	Subcutaneous	2005
Infliximab	Chimeric IgG1κ monoclonal antibody binding TNF-α	Intravenous	2005
Etanercept	Decoy TNF receptor	Subcutaneous	2002

IgG immunoglobulin G, *IL* interleukin, *IL-17RA* interleukin-17A receptor, *TNF* tumor necrosis factor

Table 2 Basic data of interleukin-23 inhibitors

Drug	Available forms	Dosing	Indications	Bioavailability (%)	Time to peak (days)	Half-life elimination (days)
Ustekinumab	Subcutaneous (90 mg/mL) or intravenous (5 mg/mL)	For patients ≤100 kg, 45 mg subcutaneously at 0 and 4 weeks, then every 12 weeks; for patients > 100 kg, 90 mg subcutaneously at 0 and 4 weeks, then every 12 weeks	Moderate-to-severe plaque psoriasis, psoriatic arthritis, moderate-to-severe Crohn's disease, and ulcerative colitis	57 [93]	13.5 (45 mg); 7 (90 mg)	14.9–45.6
Guselkumab	Subcutaneous (100 mg/mL)	100mg subcutaneously at 0 and 4 weeks, then every 8 weeks	Moderate-to-severe plaque psoriasis	49	5.5	15–18
Tildrakizumab	Subcutaneous (100 mg/mL)	100 mg subcutaneously at 0 and 4 weeks, then every 12 weeks	Moderate-to-severe plaque psoriasis	73–80	6	23
Risankizumab	Subcutaneous (75 mg/0.83 mL)	150 mg subcutaneously at 0 and 4 weeks, then every 12 weeks	Moderate-to-severe plaque psoriasis	89	3–14	28

Information from package inserts unless referenced otherwise [119–122]

2 Literature Search Methods

A literature search of PubMed was conducted for the terms "ustekinumab", "guselkumab", "tildrakizumab", and "risankizumab". Randomized controlled studies, open-label extension studies, conference abstracts, and press releases up to October 2020 were included. References of identified articles were searched for additional articles. Package inserts provided by the pharmaceutical companies producing the drugs were reviewed as well.

3 Treatment of Plaque Psoriasis

Phase II and III clinical trials investigating the efficacy of IL-23 inhibitors against placebo or comparators were identified (Tables 3, 4, 5). Primary endpoints focused on improvement from baseline Psoriasis Area and Severity Index (PASI) scores, for example, PASI 75, 90, and 100 for corresponding improvement response percentage. PASI scores are based on the extent and severity of erythema, induration, and desquamation on the head, arms, trunk, and legs. Inclusion criteria for the studies generally required diagnosis of psoriasis for 6 months involving ≥ 10% body surface area and a baseline PASI score ≥ 12.

3.1 Ustekinumab

Ustekinumab is a fully human, IgG1κ monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23. Krueger et al. first demonstrated the efficacy of ustekinumab over placebo. Three hundred and twenty patients were randomly assigned to placebo or ustekinumab (once at 45 or 90 mg, or four weekly doses at 45 or 90 mg). PASI 75 at week 12 was achieved by all treatment groups with four-weekly doses at 90 mg representing the best results at 81%. Patient-reported quality-of-life assessments were also improved with ustekinumab treatment [29].

Ustekinumab was subsequently evaluated in the phase III trials PHOENIX 1 and 2. In these trials, 1996 total patients were randomized to placebo or ustekinumab at 45 or 90 mg at 0 and 4 weeks, then every 12 weeks. The primary endpoint, PASI 75 at week 12, was met across all treatment groups in both trials with 66% and 67% at 45 mg and 66 and 76% at 90 mg. Results were consistent with the PASI 90 and 100 endpoints [30, 31]. The ACCEPT trial was conducted for a head-to-head comparison of ustekinumab with the TNF-α inhibitor etanercept. Nine hundred and seven patients were randomly assigned to receive etanercept (50 mg twice weekly) or ustekinumab (45 or 90 mg at 0 and 4 weeks, then every 12 weeks). PASI 75 at week 12 was achieved by 68% at 45 mg and 74% at 90 mg ustekinumab compared with 57% by etanercept, meeting the primary endpoint of the

Table 3 Psoriasis Area Severity Index (PASI) results of interleukin-23 inhibitors at 16 weeks

Study	Dosing or cohort	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Ustekinumab				
Krueger et al.[a] [29]	Placebo *n* = 64	1.6	1.6	0.0
	45 mg at 0 weeks *n* = 64	51.6	23.4	4.7
	90 mg at 0 weeks *n* = 64	59.4	29.7	15.6
	45 mg at 0, 1, 2, and 3 weeks *n* = 64	67.2	43.8	15.6
	90 mg at 0, 1, 2, and 3 weeks *n* = 64	81.3	51.6	20.3
PHOENIX 1[a] [30]	Placebo *n* = 255	3.1	2.0	0.0
	45 mg at 0 and 4 weeks, then every 12 weeks *n* = 255	67.1	41.6	12.5
	90 mg at 0 and 4 weeks, then every 12 weeks *n* = 256	66.4	36.7	10.9
PHOENIX 2[a] [31]	Placebo *n* = 410	3.7	0.7	0.0
	45 mg at 0 and 4 weeks, then every 12 weeks *n* = 409	66.7	42.3	18.1
	90 mg at 0 and 4 weeks, then every 12 weeks *n* = 411	75.7	50.9	18.2
ACCEPT[a] [32]	45 mg at 0 and 4 weeks, then every 12 weeks *n* = 209	67.5	36.4	NA
	90 mg at 0 and 4 weeks, then every 12 weeks *n* = 347	73.8	44.7	NA
	Comparator[b]: etanercept *n* = 347	56.8	23.1	NA
PEARL[a] [35]	Placebo *n* = 60	5.0	1.7	0.0
	45 mg at 0 and 4 weeks, then every 12 weeks *n* = 61	67.2	49.2	8.2
Igarashi et al.[a] [36]	Placebo *n* = 31	6.5	3.2	NA
	45 mg at 0 and 4 weeks, then every 12 weeks *n* = 64	59.4	32.8	NA
	90 mg at 0 and 4 weeks, then every 12 weeks *n* = 62	67.7	43.5	NA
LOTUS[a] [37]	Placebo *n* = 162	11.1	3.1	0.6
	45 mg at 0 and 4 weeks, then every 12 weeks *n* = 160	82.5	66.9	23.8
Guselkumab				
X-PLORE [40]	Placebo *n* = 42	4.8	2.4	0.0
	5 mg at 0 and 4 weeks, then every 12 weeks *n* = 41	43.9	34.1	9.8
	15 mg every 8 weeks *n* = 41	75.6	34.1	12.2
	50 mg at 0 and 4 weeks, then every 12 weeks *n* = 42	81.0	45.2	19.0
	100 mg every 8 weeks *n* = 42	78.6	61.9	33.3

Table 3 (continued)

Study	Dosing or cohort	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
	200 mg at 0 and 4 weeks, then every 12 weeks *n* = 42	81.0	57.1	28.6
	Comparator[b]: adalimumab *n* = 43	69.8	44.2	25.6
VOYAGE 1 [41]	Placebo *n* = 174	5.7	2.9	0.6
	100 mg at 0 and 4 weeks, then every 8 weeks *n* = 329	91.2	73.3	37.4
	Comparator[b]: adalimumab *n* = 334	73.1	49.7	17.1
VOYAGE 2 [42]	Placebo *n* = 248	8.1	2.4	0.8
	100 mg at 0 and 4 weeks, then every 8 weeks *n* = 496	86.3	70.0	34.1
	Comparator[b]: adalimumab *n* = 248	68.5	46.8	20.6
Ohtsuki et al. [46]	Placebo *n* = 64	6.3	0.0	0.0
	50 mg at 0 and 4 weeks, then every 8 weeks *n* = 65	89.2	70.8	32.3
	100 mg at 0 and 4 weeks, then every 8 weeks *n* = 63	84.1	69.8	27.0
ECLIPSE[a] [45]	100 mg at 0 and 4 weeks, then every 8 weeks *n* = 534	89.3	69.1	NA
	Comparator[b]: secukinumab *n* = 514	91.6	76.1	NA
ORION [48]	Placebo *n* = 16	0.0	0.0	0.0
	100 mg at 0 and 4 weeks, then every 8 weeks *n* = 62	88.7	75.8	50.0
Tildrakizumab				
Papp et al. [49]	Placebo *n* = 45	4.4	2.4	NA
	5 mg at 0 and 4 weeks, then every 12 weeks *n* = 42	33.3	12.5	NA
	25 mg at 0 and 4 weeks, then every 12 weeks *n* = 90	64.4	25.3	NA
	100 mg at 0 and 4 weeks, then every 12 weeks *n* = 89	66.3	38.6	NA
	200 mg at 0 and 4 weeks, then every 12 weeks *n* = 86	74.4	52.4	NA
reSURFACE 1[a] [50]	Placebo *n* = 154	5.8	2.6	1.3
	100 mg at 0 and 4 weeks, then every 12 weeks *n* = 309	63.8	34.6	13.9
	200 mg at 0 and 4 weeks, then every 12 weeks *n* = 308	62.3	35.4	14.0
reSURFACE 2[a] [50]	Placebo *n* = 156	5.8	1.3	0.0
	100 mg at 0 and 4 weeks, then every 12 weeks *n* = 307	61.2	38.8	12.4
	200 mg at 0 and 4 weeks, then every 12 weeks *n* = 314	65.6	36.6	11.8
	Comparator[b]: etanercept *n* = 313	48.2	21.4	4.8

Table 3 (continued)

Study	Dosing or cohort	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Risankizumab				
Papp et al.[a] [52]	18 mg at 0 weeks *n* = 43	62.8	32.6	14.0
	90 mg at 0, 4, and 16 weeks *n* = 41	97.6	73.2	41.5
	180 mg at 0, 4, and 16 weeks *n* = 42	88.1	81.0	47.6
	Comparator[b]: ustekinumab *n* = 40	72.5	40.0	17.5
UltIMMa-1 [53]	Placebo *n* = 102	9	4.9	0.0
	150 mg at 0 and 4 weeks, then every 12 weeks *n* = 304	89	75.3	35.9
	Comparator[b]: ustekinumab *n* = 100	76	42.0	12.0
UltIMMa-2 [53]	Placebo *n* = 98	6	2.0	2.0
	150 mg at 0 and 4 weeks, then every 12 weeks *n* = 294	91	74.8	50.7
	Comparator[a]: ustekinumab *n* = 99	70	47.5	24.2
SustaIMM [56]	Placebo *n* = 58	8.6	1.7	0.0
	75 mg at 0 and 4 weeks, then every 12 weeks *n* = 58	89.7	75.9	22.4
	150 mg at 0 and 4 weeks, then every 12 weeks *n* = 55	94.5	74.5	32.7
IMMvent [54]	150 mg at 0 and 4 weeks, then every 12 weeks *n* = 301	90.7	72.4	39.9
	Comparator[b]: adalimumab *n* = 304	71.7	47.4	23.0
IMMhance [57]	Placebo *n* = 100	8.0	2.0	1.0
	150 mg at 0 and 4 weeks, then every 12 weeks *n* = 407	88.7	73.2	47.2
IMMerge [55]	150 mg at 0 and 4 weeks, then every 12 weeks *n* = 164	NA	73.8	NA
	Comparator[b]: secukinumab *n* = 163	NA	65.6	NA
Mirikizumab				
Reich et al. [58]	Placebo *n* = 52	3.8	0.0	0.0
	30 mg at 0 and 8 weeks *n* = 51	52.9	29.4	15.7
	100 mg at 0 and 8 weeks *n* = 51	78.4	58.8	31.4
	300 mg at 0 and 8 weeks *n* = 51	74.5	66.7	31.4

NA not available

[a]Primary endpoint at 12 weeks

[b]Comparator drug dosed per package insert: etanercept 50 mg twice weekly; adalimumab 80 mg at 0 weeks, then 40 mg at 1 week every 2 weeks; ustekinumab 45 mg for patients weighing ≤ 100 kg at baseline or 90 mg for patients weighing > 100 kg; secukinumab 300 mg at 0, 1, 2, 3, and 4 weeks, then every 4 weeks

Table 4 Long-term Psoriasis Area Severity Index (PASI) results of interleukin-23 inhibitors in the overall population

Study (years)	Dosing or cohort	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Ustekinumab				
PHOENIX 1 (5 years) [34]	45 mg at 0 and 4 weeks, then every 12 weeks $n = 320$	63.4	39.7	21.6
	90 mg at 0 and 4 weeks, then every 12 weeks $n = 296$	72.0	49.0	26.4
PHOENIX 2 (5 years) [33]	45 mg at 0 and 4 weeks, then every 12 weeks[a]	76.5	50.0	28.1
	90 mg at 0 and 4 weeks, then every 12 weeks[a]	78.6	55.5	31.3
Guselkumab				
VOYAGE 1 (4 years) [43]	100 mg at 0 and 4 weeks, then every 8 weeks $n = 411$	93.4	82.2	55.7
VOYAGE 2 (4 years) [44]	100 mg at 0 and 4 weeks, then every 8 weeks $n = 596$	92.3	79.7	51.0
Tildrakizumab				
reSURFACE 1 (3 years) [123]	100 mg at 0 and 4 weeks, then every 12 weeks $n = 205$	84.4	57.6	24.9
	200 mg at 0 and 4 weeks, then every 12 weeks $n = 248$	75.4	50.8	25.4
reSURFACE 2 (3 years) [124]	100 mg at 0 and 4 weeks, then every 12 weeks $n = 320$	89.1	64.4	35.3
	200 mg at 0 and 4 weeks, then every 12 weeks $n = 295$	88.5	61.7	29.8
Risankizumab				
IMMhance (2 years) [57]	150 mg at 0 and 4 weeks, then every 12 weeks $n = 111$	91.0	NA	NA

NA not available

[a]Unspecified *n*

study. PASI 90 was also significantly higher in ustekinumab vs etanercept [32]. Sustained use of ustekinumab has been found to have continued efficacy for at least 5 years [33, 34].

A trio of phase III placebo-controlled trials evaluated the efficacy of ustekinumab in patients in various Asian countries. The PEARL trial was assessed in 121 Taiwanese and Korean patients randomly assigned to placebo or ustekinumab. Igarashi et al. randomized 158 Japanese patients to placebo or ustekinumab. Finally, the LOTUS trial involved 322 Chinese patients receiving placebo or ustekinumab. All three trials achieved the primary endpoint of PASI 75 at week 12, with a range of 59–83% [35–37].

The phase II trial of ustekinumab could not provide definitive conclusions about the risk profile of the drug but no unexpected findings were identified [29]. The most common adverse events reported from the PHOENIX and ACCEPT trials were upper respiratory tract infections, nasopharyngitis, arthralgia, headache, and injection-site erythema. These occurred at a similar rate between placebo and ustekinumab groups and were not dose dependent. Serious infections were rare and included cellulitis, herpes zoster, and diverticulitis [30–32]. Long-term follow-up of 5 years did not demonstrate any additional safety concerns with the overall risk profile remaining favorable. Pooled data from the phase II, PHOENIX, and ACCEPT trials found a rate of 7.1 serious events per 100 patient-years [infections (1.1), malignancy (1.1), cardiac disorders (1.1)] [38].

3.2 Guselkumab

Guselkumab is a fully human, IgG1λ monoclonal antibody targeting the p19 subunit of IL-23 [39–41]. Dosing was evaluated in the phase II trial X-PLORE comprising 293 patients randomly assigned to adalimumab (80 mg at 0 weeks, 40 mg at 1 week, then every 2 weeks) or guselkumab (5, 50, or 200 mg at 0 and 4 weeks, then every 12 weeks or 15 or 100 mg every 8 weeks; or 15 or 100 mg every 8 weeks). The primary endpoint was Physician Global Assessment score of 0 or 1 (PGA 0/1) at week 16 and achieved by all dosing groups compared with placebo [200 mg (83%), 100 mg (86%), 50 mg (79%), 15 mg (61%), 5 mg (34%), and placebo (7%)]. Similarly, all dosing groups attained a higher PASI 75, 90, and 100 than placebo. In addition, the proportion of Static Physician Global Assessment score of 0 or 1 (sPGA 0/1) was significantly higher in the 50-, 100-, and 200-mg dose groups than in the adalimumab group [40].

VOYAGE 1/2 were the first phase III trials to study guselkumab in psoriasis treatment. In total, 1829 patients

Table 5 Comparison of most frequent adverse events (AEs) at 16 weeks

AE	Ustekinumab, *n* = 556 [total number (%)][a]	Guselkumab, *n* = 494 [total number (%)]	Tildrakizumab, *n* = 1238 [total number (%)][a]	Risankizumab, *n* = 598 [total number (%)]	Mirikizumab, *n* = 153 [total number (%)]
Any AE	378 (68.0)	235 (47.6)	567 (45.8)	285 (47.7)	74 (48.4)
Serious AE	8 (1.4)	8 (1.6)	23 (1.9)	13 (2.2)	2 (1.3)
Severe AE	NA	NA	NA	13 (2.2)	NA
AE leading to drug discontinuation	8 (1.4)	7 (1.4)	11 (0.9)	3 (0.5)	NA
Death	2 (0.4)	NA	1 (0.1)	1 (0.2)	0 (0)
Nasopharyngitis	55 (9.9)	35 (7.1)	120 (9.7)	NA	
Viral URI	NA	NA	NA	30 (5.0)	19 (12.4)
URI	35 (6.3)	16 (3.2)	25 (2.0)	28 (4.7)	11 (7.2)
Headache	73 (13.1)	25 (5.1)	NA	NA	NA
Psoriasis	NA	NA	3 (0.2)	0 (0)	NA
Injection-site erythema/reaction	22 (4.0)	NA	4 (0.3)	NA	7 (4.6)
Diarrhea	NA	NA	NA	6 (1.0)	4 (2.6)
Severe infection	12 (2.2)	1 (0.2)	3 (0.2)	4 (0.7)	NA
Malignancy	4 (0.7)	0 (0)	2 (0.2)	2 (0.3)	NA
Tuberculosis	NA	NA	NA	0 (0)	NA

URI upper respiratory tract infection, *NA* not available

Ustekinumab data from ACCEPT [32]; guselkumab data from VOYAGE 2 [42]; tildrakizumab data from reSURFACE1 and 2 [50]; risankizumab data from UltIMMA-1 and -2 [53]; mirikizumab data from Reich et al. [58]

[a]Primary endpoint at 12 weeks

were randomized to receive placebo, adalimumab, or guselkumab at 100 mg at 0 and 4 weeks, then every 8 weeks. The primary endpoint was compared to placebo and evaluated by an Investigator Global Assessment (IGA) score 0 or 1 at week 16 achieved by 84–85%; PASI 90 was coprimary and achieved by 70–73%. Guselkumab was also superior to adalimumab at these endpoints. In addition, guselkumab showed significant improvement in scalp, nail, and extremity disease as well as quality-of-life measures [41, 42]. For the VOYAGE trials, high efficacy rates were sustained for 4 years [43, 44].

Guselkumab was directly compared to the IL-17 inhibitor secukinumab in the ECLIPSE trial. The comparator-controlled trial randomized 1048 patients to secukinumab or guselkumab at 100 mg at 0 and 4 weeks, then every 8 weeks. PASI 75 and 90 scores response rates were similar at 12 weeks, displaying short-term non-inferiority; however, the primary endpoint of PASI 90 at week 48 demonstrated superior long-term efficacy of guselkumab over secukinumab with 84% vs 70% (non-inferiority test $p < 0.0001$, superiority test $p < 0.0001$) [45].

Ohtsuki et al. also investigated guselkumab in a phase III trial of Japanese patients with 192 patients receiving either placebo or guselkumab. The efficacy of guselkumab was confirmed in this trial with primary endpoints at week 16 of IGA 0/1 and PASI 90 achieved [46]. In the NAVIGATE trial, guselkumab also demonstrated potential as an alternative to ustekinumab treatment. Patients with inadequate response to ustekinumab, as defined by a failure to achieve IGA 0/1 by week 16, showed significant improvement upon switching to guselkumab [47]. The ORION study evaluated the use of a novel convenient patient-controlled injector confirming comparable efficacy and safety with alternate administration. Importantly, patient questionnaires indicated high satisfaction rates with use of the device [48].

There was no evidence of dose dependence in the rate of adverse events in the guselkumab group from the weeks 0 to 16 in the X-PLORE trial. Furthermore, the patient proportions with one or more adverse events were 52%, 50%, and 56% for the placebo group, guselkumab groups and adalimumab group, respectively. From weeks 16 to 52, three patients in the guselkumab group were observed to have major adverse cardiovascular events (MACE) compared to none in the adalimumab group [40]. Similar results were seen in the VOYAGE trials with the most common adverse events being nasopharyngitis, upper respiratory tract infection, injection-site erythema, headache, arthralgia, pruritus, and back pain [41, 42]. Guselkumab was confirmed to be well tolerated in subsequent phase III trials as well. Malignancy was rarely observed with the majority representing non-melanoma skin cancers. Serious infections were also occasionally seen, including skin abscesses, cellulitis,

appendicitis; active tuberculosis (TB) was not identified [45, 46]. Long-term observation of guselkumab resulted in no unexpected safety findings after 4 years [43, 44].

3.3 Tildrakizumab

Tildrakizumab is a humanized IgG1κ monoclonal antibody that binds and inhibits the p19 subunit of IL-23 [49]. Dose ranging and efficacy of tildrakizumab was identified by Papp et al. in a phase II trial. Three hundred and fifty-five patients were randomly assigned to placebo or tildrakizumab dosed at 5, 25, 100, or 200 mg at 0 and 4 weeks, then every 12 weeks. The primary endpoint of PASI 75 was met by all dosing groups [200 mg (74.4%), 100 mg (66.3%), 25 mg (64.4%), 5 mg (33.3%), and placebo (4.4%)]. sPGA 0/1 was also achieved by all groups and PASI 90 was achieved by all groups except for the 5-mg group. Patients in the 100- and 200-mg groups sustained high levels of efficacy through week 52 and week 72 after discontinuation at week 52 [49].

A phase III study of tildrakizumab at 100- and 200-mg doses ensued in the reSURFACE trials. In reSURFACE 1, 772 patients were randomly assigned to placebo or tildrakizumab. Co-primary endpoints of PGA 0/1 and PASI 75 were assessed at week 12. PGA 0/1 was achieved by 58 and 59% in the 100- and 200-mg groups and PASI 75 was achieved by 62 and 64% at 100 and 200 mg. In reSURFACE 2, 1090 patients were additionally randomized to an etanercept group. PGA 0/1 was met by 61 and 66% at 100 and 200 mg compared with 48% taking etanercept, while PASI 75 was met by 55 and 59% at 100 and 200 mg compared with 48% taking etanercept [50]. Furthermore, PASI 75 and 90 responses were shown to be maintained through 3 years. In 60% of cases, partial responders at week 28 actually achieved PASI 75 by week 52 [51].

Tildrakizumab had a similar safety profile to guselkumab with nasopharyngitis, headache, and injection-site reaction representing the most common adverse events from the phase II study [49]. Serious adverse events occurred at similar frequencies across all tildrakizumab groups and were found to remain at a low incidence after nearly 3 years for those treated with tildrakizumab [50, 51].

3.4 Risankizumab

Risankizumab is a humanized IgG1 monoclonal antibody directed against the p19 subunit of IL-23 [52]. Papp et al. first investigated risankizumab in a phase II study involving 166 patients randomized to ustekinumab at standard doses or risankizumab at 18 mg at 0 weeks or 90 or 180 mg at 0, 4, and 16 weeks. The primary endpoint, PASI 90, was achieved by the 90- and 180-mg groups with 73 and 81%, respectively, compared with 40% in the ustekinumab group. In addition, risankizumab showed sustained and superior efficacy to ustekinumab in the treatment of scalp, fingernail, and palmoplantar disease [52].

These results were followed by the UltIMMA-1 and -2 phase III studies. In these trials, 997 total patients were randomly assigned to placebo, ustekinumab, or risankizumab at 150 mg at 0 and 4 weeks, then every 12 weeks. Primary endpoints were assessed at week 16 by sPGA 0/1 and PASI 90. The sPGA endpoint was achieved by 84–88% on risankizumab compared with 62–63% on ustekinumab and PASI 90 was achieved by 75% compared to 42–48%. The secondary endpoint, PASI 75, was attained by 89–91% compared to 70–76% on ustekinumab [53]. The phase III trial IMMvent subsequently compared the efficacy of risankizumab and the TNF-α inhibitor adalimumab. In this trial, 605 patients were randomly assigned to adalimumab or risankizumab (150 mg at 0 and 4 weeks, then every 12 weeks). Similarly, all primary and secondary endpoints were achieved. The sPGA 0/1 and PASI 90 were attained by 84 and 72% of risankizumab-treated patients compared with 60 and 47% of adalimumab-treated patients, respectively [54].

Finally, the IMMerge phase III trial directly compared risankizumab (150 mg at 0 and 4 weeks, then every 12 weeks) with the IL-17 inhibitor secukinumab in 327 patients. The primary endpoint, PASI 90 at week 16, was achieved by 74% in the risankizumab group compared with 66% in the secukinumab group, demonstrating short-term non-inferiority. Furthermore, PASI 90 at week 52 was attained by 87% of risankizumab-treated patients vs 57% of secukinumab-treated patients, displaying superior long-term efficacy [55].

The SustaIMM study was a phase II/III trial conducted in 171 Japanese patients, confirming the efficacy of risankizumab (75 or 150 mg at 0 and 4 weeks, then every 12 weeks) compared with placebo. All primary and secondary endpoints were met with PASI 90 at week 16 achieved by 75 and 76% at the 75 and 150 mg doses of risankizumab [56]. The phase III, 2-year trial IMMhance further confirmed this with 507 patients randomly assigned to placebo or risankizumab at 150 mg at 0 and 4 weeks, then every 12 weeks. The primary endpoints PASI 90 and sPGA 0/1 at week 16 were met by 73 and 84% vs 2 and 7%. Notably, risankizumab response was sustained throughout the duration of the trial [57].

The most common adverse events seen in those taking risankizumab were nasopharyngitis, headache, gastroenteritis, and back pain [52]. Subsequent phase III trials also did not find any unexpected safety findings. Additional common adverse events that were reported include upper respiratory tract infections, diarrhea, and arthralgia. Overall, the frequency of serious events, including MACE, infection, and malignancy, was similar among all treatment groups and reflected baseline risks in patients with psoriasis. The IMMhance trial confirmed a favorable risk profile that was further maintained through the 2-year trial [57].

3.5 Developmental

Mirikizumab is a humanized IgG4 monoclonal antibody targeting the p19 subunit of IL-23 [58]. Mirikizumab was first evaluated in a 2019 phase II study comprising 205 patients. Treatment groups were divided into doses of 30, 100, or 300 mg given at 0 and 8 weeks, all of which displayed significant improvement in PASI 90 as compared with placebo. Both the 100- and 300-mg groups demonstrated higher PASI 90 compared with the 30-mg group, attaining 59 and 67%, respectively. PASI 75 and 100 were also significantly higher with mirikizumab treatment compared with placebo [58].

A series of phase III trials are underway studying the efficacy and safety of mirikizumab in the treatment of psoriasis, including in the long term (OASIS-1/2/3; NCT03482011, NCT03535194, NCT03556202). Recently, Lilly announced early results of the OASIS-2 study, comparing mirikizumab with the IL-17 inhibitor secukinumab. The study randomly assigned 1465 patients to placebo, secukinumab (300 mg at 0, 1, 2, 3, and 4 weeks, then every 4 weeks), and mirikizumab (250 mg at 0, 4, 8, and 12 weeks, then every 8 weeks; or 250 mg at 0, 4, 8, and 12 weeks, then 125 mg every 8 weeks). Preliminary results indicated non-inferiority at week 16 and superiority at week 52 of mirikizumab compared with secukinumab. PASI 90 at week 16 was achieved by 74.4% of mirikizumab-treated patients compared with 72.8% of secukinumab-treated patients. In addition, sPGA 0/1 was achieved by 79.7% in the mirikizumab group compared with 76.3% in the secukinumab group [59].

As yet, the safety profile of mirikizumab is similar to the other IL-23 inhibitors. The most common adverse events reported from Reich et al. and OASIS-2 were nasopharyngitis, upper respiratory tract infection, injection-site pain, hypertension, and diarrhea. Overall frequency of serious adverse events did not differ between treatment groups [58, 59]. Brazikumab is a human IgG2 monoclonal antibody targeting the p19 subunit of IL-23 that has been studied for use in Crohn's disease but has yet to be investigated in the treatment of psoriasis [60].

4 Treatment of Psoriatic Arthritis

Interleukin-23 inhibitors have also been studied in phase II and III trials of PsA (Table 6). Primary endpoints of these trials examined the American College of Rheumatology 20 (ACR20), which measures the proportion of patients with at least a 20% improvement from baseline. Secondary endpoints included ACR50 and ACR 70. The ACR score is assessed based on pain, physical functioning, and acute-phase reactant levels. Inclusion criteria for the trials included active PsA (varied, but generally ≥ 3–5 swollen joints, ≥ 3–5 tender joints, and a threshold C-reactive protein level) and active psoriasis (target lesion ≥2 cm and inadequate response to therapy other than biologic drugs).

4.1 Ustekinumab

Ustekinumab was approved for the treatment of PsA in 2013. An initial phase II trial randomly assigned 146 patients to placebo or ustekinumab (17 patients received the 90-mg dose, after which filtration procedure was implemented, resulting in remaining 59 patients to receive the 63-mg dose). The primary endpoint of ACR 20 was assessed at week 12 achieved by 42% of patients receiving ustekinumab. Secondary endpoints of ACR50 and ACR70 at week 12 were achieved by 25 and 11% [61].

The PSUMMIT 1/2 phase III study followed with 927 total patients randomly assigned to placebo or ustekinumab at 45 or 90 mg at 0 and 4 weeks, then every 12 weeks. At week 24, the primary endpoint of ACR20 was achieved by 42–44% at 45 mg and 44–50% at 90 mg. Similarly, the ACR50 was achieved by 18–25% at 45 mg and 23–28% at 90 mg and the ACR70 was achieved by 7–12% at 45 mg and 9–14% at 90 mg. Radiographic progression of disease was also significantly reduced through 52 weeks in the ustekinumab group [62, 63]. The ECLIPSA trial directly compared ustekinumab with TNF-α inhibitors in treating enthesitis, demonstrating achievement of primary endpoint of clearance of enthesitis [64]. Ustekinumab was also assessed in axial spondyloarthritis in three trials, the latter two of which were discontinued after primary and secondary endpoints were not met in the first trial [65].

4.2 Guselkumab

Guselkumab was recently approved by the FDA as the first selective IL-23 inhibitor for the treatment of PsA [66]. Guselkumab first showed efficacy in a phase II study randomizing 149 patients to placebo or guselkumab at 100 mg at 0 and 4 weeks, then every 8 weeks. The primary endpoint, ACR20 at week 24, was achieved by 58% of patients receiving guselkumab compared with 18% of patients receiving placebo. The ACR50 and ACR70 secondary endpoints also demonstrated significant improvement of 34 and 14% in the guselkumab group compared with 10 and 2% in the placebo group. ACR20 and ACR50 were achieved as early as week 16 [67].

The DISCOVER-1/2 phase III studies involved 1122 total patients randomly assigned to guselkumab (100 mg at 0 and 4 weeks, then every 8 weeks; or 100 mg every 4 weeks) or placebo. The primary endpoint of ACR20 at week 24 was achieved by 52 and 64% of guselkumab-treated patients in the trials compared with 22 and 23% of placebo-treated patients. Secondary endpoints, including ACR50 and ACR70 at week 24, were also achieved.

Table 6 American College of Rheumatology results of interleukin-23 inhibitors at 24 weeks

Study	Dosing or cohort	ACR20 (%)	ACR50 (%)	ACR70 (%)
Ustekinumab				
Gottlieb et al.[a] [61]	Placebo $n = 70$	14.3	7.1	0.0
	90 mg or 63 mg at 0, 1, 2, and 3 weeks[b] $n = 76$	42.1	25.0	10.5
PSUMMIT 1 [62]	Placebo $n = 206$	22.8	8.7	2.4
	45 mg at 0 and 4 weeks, then every 12 weeks $n = 205$	42.4	24.9	12.2
	90 mg at 0 and 4 weeks, then every 12 weeks $n = 204$	49.5	27.9	14.2
PSUMMIT 2 [63]	Placebo $n = 104$	20.2	6.7	2.9
	45 mg at 0 and 4 weeks, then every 12 weeks $n = 103$	43.7	17.5	6.8
	90 mg at 0 and 4 weeks, then every 12 weeks $n = 105$	43.8	22.9	8.6
Guselkumab				
Deodhar et al. [67]	Placebo $n = 49$	18.4	10.2	2.0
	100 mg at 0 and 4 weeks, then every 8 weeks $n = 100$	58.0	34.0	14.0
DISCOVER-1 [68]	Placebo $n = 126$	22.2	8.7	5.6
	100 mg every 4 weeks $n = 128$	59.4	35.9	20.3
	100 mg at 0 and 4 weeks, then every 8 weeks $n = 127$	52.0	29.9	11.8
DISCOVER-2 [69]	Placebo $n = 246$	32.9	14.2	4.1
	100 mg every 4 weeks $n = 245$	63.7	33.1	13.1
	100 mg at 0 and 4 weeks, then every 8 weeks $n = 248$	64.1	31.5	18.5

[a]Primary endpoint at 12 weeks

[b]17/76 patients received 90 mg; remaining patients received a filtered dose equivalent to 63 mg

In addition, guselkumab was significantly beneficial for improving physical functioning, enthesitis, dactylitis, and fatigue [68, 69]. Pooled analysis of the DISCOVER trials found resolution of enthesitis by 45–50% of the guselkumab group compared with 29% of placebo and resolution of dactylitis by 59–64% of the guselkumab group compared with 42% of placebo; baseline scores were also significantly decreased after 24 weeks of treatment [69]. Similar efficacy in dactylitis and enthesitis was seen through 56 weeks in a phase II trial of patients with active PsA despite current or previous conventional therapy [70].

4.3 Developmental

Tildrakizumab and risankizumab remain in the trial phase for evaluation of their efficacy in PsA. Initial subset analyses of 65 patients with PsA in a phase II trial of tildrakizumab in the treatment of psoriasis showed an improved, but not necessarily statistically significant, change in ACR components and PsA endpoints such as the Psoriatic Arthritis Screening and Evaluation, Health Assessment Questionnaire, pain assessed with the Visual Analog Scale, and high-sensitivity C-reactive protein (NCT01225731) [71]. A recent case

report in Australia described a patient with improvement of PsA within 9 weeks after subcutaneous administration at 0 and 4 weeks [72]. A phase IIb trial randomized 391 patients to receive tildrakizumab (200 mg every 4 weeks, 200 mg every 12 weeks, 100 mg every 12 weeks, or 20 mg every 12 weeks) or placebo. Preliminary results showed clear efficacy of tildrakizumab in the treatment of PsA as compared to placebo with differences detected in ACR20 and ACR50 at 12 weeks in the 200-mg dose groups (NCT02980692) [73].

Risankizumab has been evaluated in a phase II trial with 185 patients randomized to risankizumab (150 mg every 4 weeks; 150 mg at 0 and 4 weeks, then every 12 weeks; 150 mg every 12 weeks; or 75 mg at 0 weeks) or placebo. Preliminary results demonstrated superior ACR20, ACR50, and ACR70 scores in all risankizumab dosage groups as compared with placebo (NCT02719171) [74]. Meanwhile, a phase III trial series is currently underway to compare risankizumab with placebo in the treatment of PsA (KEEPsAKE1/2; NCT03671148). Risankizumab was also assessed for efficacy in ankylosing spondylitis, but similar to ustekinumab failed to meet the primary endpoint [75].

5 Discussion

Interleukin-23 inhibitors represent safe and effective options in the treatment of patients with psoriasis and psoriatic arthritis. As reflected by their primary endpoints, clinical trials demonstrate the superior efficacy of IL-23 inhibitors to traditional forms of therapy, including TNF-α inhibitors. Guselkumab and risankizumab may particularly stand out (Fig. 1); however, comparison of efficacy among the IL-23 inhibitors has been mixed. Sawyer et al. performed a network meta-analysis that showed guselkumab and risankizumab were superior to tildrakizumab [76]. In contrast, Du Jardin et al. performed an indirect comparison of guselkumab and tildrakizumab and found no significant difference in efficacy at short-term time points [77]; of note, their analysis did not include phase II trials. The investigators of the reSURFACE trials noted that the 12-week primary endpoint (two doses) may have been too early for adequate evaluation of tildrakizumab compared to the 16-week endpoint (three doses) for the other two drugs [50]. A study by AbbVie showed that guselkumab and risankizumab are high-affinity antibodies acting by competitive inhibition, whereas tildrakizumab is a negative allosteric modulator with high off-rates; as a result, risankizumab was found to have a three-fold higher potency compared with guselkumab and a 50-fold higher potency compared with tildrakizumab [78]. As more long-term data become available, more head-to-head comparisons will be necessary.

The IL-23 inhibitors have also been shown to lead to a long duration of remission after withdrawal of the drug. In trials of TNF-α inhibitors, the median time to loss of PASI 50 had a range of 12.1–19.5 weeks after discontinuation of therapy [79]. In contrast, median time to loss of PASI 50 in the PHOENIX 1 trial for ustekinumab was estimated to be about 22 weeks from the last dose [30, 79]. In the VOYAGE 2 trial, 182 out of 375 patients were randomized to guselkumab withdrawal with a median time to loss of PASI 90 at 23 weeks after the last dose [42]. The median time to loss of PASI 90 in the reSURFACE 2 trial was 28 and 32 weeks after the last dose of tildrakizumab 100 and 200 mg [80]. Finally, the median time loss of PASI 90 was 42 weeks after the last dose with risankizumab in the IMMhance trial [57]. While response remains superior with maintenance of therapy, IL-23 inhibitors show a sustained level of efficacy even after discontinuation for several months.

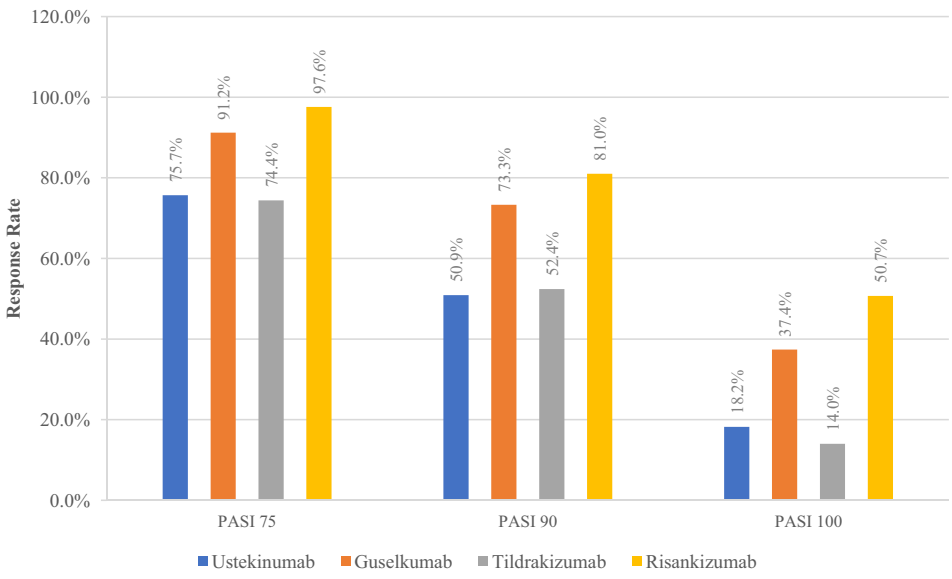

Fig. 1 Comparison of best Psoriasis Area and Severity Index (PASI) 75/90/100 responses from phase III results. Ustekinumab data from ACCEPT trial [32]; guselkumab data from VOYAGE 1 [41]; tildrakizumab data from Papp et al. and reSURFACE 1 [49, 50]; risankizumab data from Papp et al. and UltIMMa-1 [52, 53]. LOTUS and ORION trial results were not compared because of differences in baseline data and treatment administration

Similarly, selective targeting of IL-23 results in strong improvement of PsA. ACR20 and ACR50 response rates were significantly higher in studies of ustekinumab and guselkumab compared with placebo with promising preliminary results in tildrakizumab and risankizumab. Further studies evaluating the effectiveness of IL-23 inhibitors against other classes are needed, as anti-IL-23 therapy represents a fourth-line option behind treatments with better evidence. The 2018 ACR/National Psoriasis Foundation guidelines support the first-line use of TNF-α inhibitors in new active PsA, followed by oral small molecules, such as methotrexate or sulfasalazine, IL-17 inhibitors, and finally IL-12/IL-23 inhibitors (specific IL-23 inhibitors were not FDA approved yet) [81]. Some variations exist depending on contraindications or comorbidities, such as using IL-17 and IL-23 inhibitors in patients with concomitant severe psoriasis. As more data become available on the efficacy of IL-23 inhibitors, they may be used more in PsA treatment.

Targeting of IL-23 has emerged with an improved understanding of the role of the IL-23/Th17 axis in the development of psoriasis. Early investigation of skin samples from patients with psoriasis showed increased expression levels of IL-23 [20, 82]. Further studies elucidated the role of IL-23 activation of Th17 and subsequent production of pro-inflammatory cytokines including IL-17, TNF-α, IL-26, and IL-29 that contribute to epidermal hyperplasia and recruitment of immune cells [83]. Interleukin-23 inhibition was first shown to be effective by Sofen et al. demonstrating histopathological improvement with a reduction in levels of IL-17 [39]. The efficacy of IL-23 blockade was further supported by reduction in IL-17 and IL-22 levels through the sequestration of IL-23 by a decoy protein containing the IL-23 receptor cytokine-binding homology region [84]. Such evidence provides support for potential development of an IL-23 receptor-Fc fusion protein, similar to etanercept [85].

A major advantage of IL-23 inhibitors is that targeting of upstream cytokines requires less frequent dosing compared with targeting of downstream cytokines such as IL-17 and TNF-α [86]. In addition, studies of IL-23 and IL-17 inhibitors to this point have shown sustained strong efficacy at 1 year and beyond [43, 44, 48, 87, 88]. A network meta-analysis of PASI response demonstrated that the short-term efficacy of IL-17 inhibitors, particularly ixekizumab and brodalumab, and IL-23 inhibitors, particularly guselkumab and risankizumab, were similar [76]. However, IL-17 inhibitors are superior in achieving a more rapid response, as seen in a head-to-head trial of ixekizumab and guselkumab [89]. As more long-term data become available, comparison of efficacy will be needed for further assessment. In the meantime, selection of these drugs should involve a discussion of patient preferences for care.

Notably, specific inhibition of IL-23 shows evidence of superiority compared with the anti-IL-12/23 action of ustekinumab. The phase II trial conducted by Papp et al. and the phase III trial UltIMMa-1/2 both demonstrated improved efficacy of risankizumab compared with ustekinumab [52, 53]. Preservation of IL-12 activation of T helper 1 response is thought to allow for interferon-γ protection against intracellular pathogens, such as *Mycobacterium* species, *Salmonella*, *Pneumocystis jirovecii*, and *Toxoplasmosis gondii* [90, 91]. Further, IL-12 is unlikely to have a significant role in the pathogenesis of psoriasis [20]. However, UltIMMa-1/2 reported similar rates of adverse events including infections between ustekinumab and risankizumab treatment. The benefit of risankizumab over ustekinumab may not be completely attributed to improved pathogenic immunity and further comparison studies would be useful.

Safety profiles of IL-23 inhibitors to this point appear to be relatively benign with all classes most commonly possessing adverse events including nasopharyngitis, upper respiratory tract infection, headache, and backache. Most serious adverse events, including serious infection, MACE, malignancy, and death, that were observed in the clinical trials were in line with the expected proportions observed in the general population of patients with psoriasis. In many cases, patients already had pre-existing risk factors that predisposed them to the development of adverse events [92]. Drug-interaction studies conducted on these drugs have shown little to no effect on cytochrome P450 enzymes, further supporting a positive safety profile [93–96]. Given the novelty of these drugs, long-term studies to carefully monitor for the development of more serious side effects are naturally required. Of note is the risk of serious infection and reactivation of diseases such as TB in light of immune system modulation, as seen in TNF-α inhibitors [97]. However, IL-23 inhibitors were not shown to increase the risk for TB infection or reactivation. A recent review of IL-17 inhibitors also showed no cases of TB reactivation in patients with psoriasis treated with an IL-17 inhibitor [98]. It has been posited that IL-23 and IL-17 do not necessarily protect against TB, but they may be more involved in regulating inflammation in this setting [99]. However, routine annual monitoring for a potential TB infection is still recommended. In addition, multiple studies demonstrated that co-therapy with isoniazid to treat for latent TB did not change the efficacy or safety of IL-23 therapy [100, 101].

While the ustekinumab trials have not shown significantly more cardiovascular events compared to placebo, the association of IL-12/23 inhibitors and such events has remained controversial [102–104]. In particular, briakinumab was another IL-12/23 inhibitor that was withdrawn from FDA application after a phase III trial showed a significantly increased risk of MACE [105]. Despite the lack of conclusive data describing the risk of ustekinumab, patient discussion about risk factors and avoidance of the drug has been favored [106]. More recently, a French

retrospective case-time-control study compared the risk of acute coronary syndrome or stroke in the 6 months before and after initiation of ustekinumab. The study found an increased risk for these events in patients considered high cardiovascular risk (two risk factors or personal history of acute coronary syndrome or stroke), positing a role for IL-17 in stabilizing atherosclerotic plaques [107]. In consideration of the latest study, mindful evaluation of risk factors such as hypertension, hyperlipidemia, and diabetes mellitus is important and alternatives to ustekinumab should be identified in high-risk patients.

The outbreak of Coronavirus Disease 2019 (COVID-19) has raised additional questions about the use of biologic drugs during a pandemic. Based on trial data, Lebwohl et al. found slight absolute increases, up to 9%, in overall infection risk with IL-23 inhibition, but these cannot necessarily be extrapolated to COVID-19 risk [108]. Furthermore, the immune response to viral infections is known to involve multiple mediators in the innate and adaptive immune systems. As IL-23 does not represent a significant factor in this response, viral clearance may not be significantly impaired by targeted therapy. Patients should be counseled on the possibility of an increased risk of COVID-19 infection and most may be able to continue therapy in the absence of severe symptoms [109].

While IL-17 inhibition is thought to be linked to new or exacerbated inflammatory bowel disease, IL-23 targeting is not associated with such a risk profile. In fact, IL-23 inhibitors are being investigated with promising efficacy to treat inflammatory bowel disease, and ustekinumab is already FDA approved to treat Crohn's disease [110, 111]. Similarly, IL-17 is key for immunity against *Candida* infection and rarely reported with targeting of IL-17, but not IL-23 [112].

The risks of treating psoriasis with biologic drugs in patients with underlying conditions require careful attention (Tables 7, 8). While limited data exist overall on the safety and efficacy on IL-23 inhibitors in these populations, similar caution may be taken in the initiation of these drugs as with TNF-α inhibitors. According to the joint American Academy of Dermatology-National Psoriasis Foundation guidelines for the management and treatment of psoriasis with biologic drugs, baseline laboratory studies prior to initiating IL-23 inhibitor therapy include complete blood count, complete metabolic profile, TB test (PPD or Quantiferon Gold), hepatitis B virus and hepatitis C virus serology, and human immunodeficiency virus test. In addition, periodic testing for TB, hepatitis B virus, hepatitis C virus, other

Table 7 Considerations in special populations

Drug	Pregnancy category	Lactating	Pediatric	Geriatric
Ustekinumab	B	Insufficient data	Approved in patients aged ≥ 6 years	No differences observed in limited data
Guselkumab	Insufficient data	Insufficient data	Insufficient data	No differences observed in limited data
Tildrakizumab	Insufficient data	Insufficient data	Insufficient data	No differences observed in limited data
Risankizumab	Insufficient data	Insufficient data	Insufficient data	No differences observed in limited data

Information from package inserts unless referenced otherwise [119–122]

Table 8 Considerations in infections and malignancy

Drug	HIV	HBV	HCV	TB	Underlying malignancy
Ustekinumab	Safe and effective in limited data; combine with ART and monitor closely [98, 99]	Assess HBV serology	Assess HCV status	Assess TB status; avoid in active TB; treat latent TB first	Screening for skin cancer
Guselkumab	Safe and effective in 1 case; monitor closely and consider ART [98]	Assess HBV serology; safe and effective in 1 case [104]	Assess HCV status	Assess TB status; avoid in active TB; treat latent TB first	Screening for skin cancer
Tildrakizumab	Insufficient data	Assess HBV serology	Assess HCV status	Assess TB status; avoid in active TB; treat latent TB first	Screening for skin cancer
Risankizumab	Insufficient data	Assess HBV serology	Assess HCV status	Assess TB status; avoid in active TB; treat latent TB first	Screening for skin cancer

ART anti-retroviral therapy, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *TB* tuberculosis

Information from package inserts unless referenced otherwise [119–122]

infections, and skin cancer should be implemented with variable frequency depending on individual patient risks [113]. It is recommended to treat patients for active or latent TB prior to the onset of therapy. Limited data show that ustekinumab treatment in patients with active or latent hepatitis B virus or hepatitis C virus is safe and effective and is not associated with an increased rate of reactivation [114–116]. In patients with human immunodeficiency virus, no differences in efficacy have been observed in a few cases of ustekinumab treatment and one case of guselkumab treatment; no data exist for tildrakizumab and risankizumab treatment [117, 118]. The data in pregnant and lactating patients are limited and no FDA pregnancy category has been assigned to these drugs.

6 Conclusions

The wealth of research on the pathogenesis of psoriasis has unlocked new classes of drugs that redefine how psoriasis and PsA are treated. As the role of the IL-23/Th17 axis has become further uncovered, targeted therapy of IL-23 has rapidly risen to the forefront to set a new standard for psoriasis outcomes. Over the last 3 years, guselkumab, tildrakizumab, and risankizumab have successively come to the market, showing superior efficacy and favorable safety profiles compared to existing medications.

Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material All data and material are included in the article.

Code availability Not applicable.

Author contributions BEE and ASO conceptualized and designed the study. KY gathered data for the manuscript, and wrote the initial draft of the manuscript. All authors read and approved the final manuscript.

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