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IL-17 Inhibition vs IL-23 Inhibition for Psoriatic Arthritis: An Ongoing Debate

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Abstract

The interleukin-17 (IL-17) and interleukin-23 (IL-23) pathways play a central role in the pathogenesis of psoriatic disease (PsD). This review outlines the immunobiology of these cytokine pathways and summarizes the current evidence on the efficacy and safety of IL-17 and IL-23 inhibitors across PsD domains, including peripheral arthritis, axial arthritis, enthesitis, dactylitis, psoriasis, and inflammatory bowel disease (IBD). IL-17 inhibitors, which target the effector cytokines IL-17A, IL-17F, or their receptors, have demonstrated robust efficacy in psoriasis, peripheral arthritis, and axial disease. IL-23 inhibitors act upstream by targeting the p19 subunit of IL-23 and show comparable efficacy in peripheral arthritis and psoriasis, though evidence for efficacy in axial disease remains limited. While IL-17 inhibitors carry a risk of IBD exacerbation, IL-23 inhibitors are considered therapeutic options for patients with coexisting IBD. In addition, radiographic progression appears better suppressed by IL-17 inhibitors, although emerging data suggest that IL-23 blockade may offer delayed benefits. Both IL-17 and IL-23 drug classes exhibit favourable safety profiles, with clinical trials suggesting slightly better tolerability for IL-23 inhibitors. Future directions include head-to-head comparisons, biomarker-guided treatment selection, and trials assessing long-term structural outcomes. Understanding the tissue- and cell-specific effects of inhibiting these cytokine pathways is key to optimizing therapy in PsD.

Introduction

Psoriatic disease (PsD) is a chronic, immune-mediated condition encompassing a spectrum of manifestations including psoriasis, psoriatic arthritis (PsA), enthesitis, and extra-musculoskeletal features such as uveitis and inflammatory bowel disease (IBD).[1] Psoriasis and PsA often coexist, with over 70% of PsA cases preceded by cutaneous psoriasis.[1,2] Both conditions share overlapping immunopathogenic mechanisms, prominently involving dysregulated type 3 immunity.[3]

Recent advances in understanding this pathway have revolutionized the therapeutic landscape for PsD over the past decade. A range of targeted biologic agents are now available, including inhibitors of interleukin (IL)-23p19, IL-12/23p40, IL-17A, the IL-17 receptor, and dual IL-17A/F. IL-23, produced by innate immune cells, promotes the differentiation and maintenance of T-helper (Th) 17 cells, which in turn secrete IL-17, a central cytokine driving tissue inflammation.[4]

Although both IL-23 and IL-17 inhibitors modulate the type 3/Th17 immune response, their mechanisms of action differ: IL-23 inhibitors act upstream by modulating the survival and function of Th17 cells, while IL-17 inhibitors directly block the downstream effector cytokine. These mechanistic differences contribute to variations in clinical efficacy across disease domains, onset of action, safety profiles, and suitability for specific patient subsets. As a result, the optimal choice of therapy, especially in patients with multi-domain disease, remains a subject of ongoing debate.

In this review, we explore the immunologic rationale behind IL-23 and IL-17 inhibition and critically appraise the clinical efficacy, safety, and practical considerations associated with using these therapies in managing PsD. Gaining a nuanced understanding of these distinctions is vital for guiding personalized treatment decisions in this heterogeneous disease.

Drugs Targeting the IL-23-IL-17 Pathway

Therapeutic agents targeting the IL-23/IL-17 axis fall broadly into two categories based on their mechanism of action:

IL-17 inhibitors act downstream by directly blocking effector cytokines of Th17-mediated inflammation. These include:

- Secukinumab and ixekizumab, monoclonal antibodies (mAbs) that selectively neutralize IL-17A.
- Brodalumab, an mAb that blocks the IL-17 receptor A (IL-17RA), thereby inhibiting signalling from multiple IL-17 family cytokines, including IL-17A and IL-17F.
- Bimekizumab, a unique monoclonal antibody that neutralizes both IL-17A and IL-17F, providing broader inhibition of IL-17-mediated pathways.

IL-23 inhibitors act upstream by targeting the p19 subunit of IL-23, which is essential for the survival and proliferation of Th17 cells. This group includes:
Guselkumab, risankizumab, tildrakizumab, and mirikizumab (currently under investigation), all of which selectively inhibit IL-23 by binding to its p19 subunit. Notably, guselkumab also has a unique mechanism involving the CD64 receptor on IL-23-producing myeloid cells. Guselkumab's native Fc domain allows it to bind to the CD64 receptor, leading to internalization and trafficking of IL-23 to endolysosomal compartments, potentially enhancing its neutralization at the source.

Additionally, ustekinumab targets the shared p40 subunit of IL-12 and IL-23, thereby affecting both Th1 and Th17 pathways. However, this review will focus on the first two groups **(Figure 1)**.

Clinical Efficacy Across Various Domains of Psoriatic Arthritis

Given the heterogeneous nature of PsD, which can involve the skin, nails, eyes, musculoskeletal system, and gastrointestinal tract, the choice of therapy is driven by multiple factors. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommends a domain-based approach to both patient assessment and treatment selection. This strategy emphasizes targeting the most active disease domain while considering the impact of involvement across other domains.[5]

Musculoskeletal Domains

- **Peripheral arthritis:** IL-17 inhibitors have demonstrated strong efficacy in treating peripheral arthritis. Across the FUTURE 1–5 trials, secukinumab achieved American College of Rheumatology (ACR)20 response rates ranging from 40–54% compared to 15–21% for placebo.[6-9] Efficacy varied based on dosage, mode of administration, and prior exposure to tumour necrosis factor (TNF) inhibitors. Ixekizumab demonstrated similar effectiveness. In TNF inhibitor-naïve patients (SPIRIT-P1), the ACR20 response at week 24 was 57.9% versus 30.2% for placebo.[10] In TNF inhibitor-experienced patients (SPIRIT-P2), ACR20 responses at week 24 were 53% versus 20%.[11] Brodalumab, evaluated in the AMVISON 1 and 2 trials, demonstrated ACR20 responses of approximately 46% at week 16 versus 20.09 % with placebo in biologic disease-modifying antirheumatic drug (bDMARD) naïve patients with active PsA. However, these trials were discontinued due to concerns over psychiatric adverse effects.[12,13] Bimekizumab, the most recently approved IL-17 inhibitor, has shown impressive outcomes. In TNF inhibitor-naïve patients (BE OPTIMAL), ACR50 responses at week 16 were 44% versus 10% with placebo.[14] In TNF inhibitor-experienced patients (BE COMPLETE), ACR50 responses at week 16 were 43% versus 7%.[15] IL-23 inhibitors have also shown comparable efficacy in PsA. Guselkumab was the first IL-23 inhibitor approved for PsD. In the DISCOVER 1 trial, ACR20 responses at week 24 ranged from 52-59% based on dosing, compared to 22% with placebo in both TNF inhibitor-naïve and experienced patients.[16] The DISCOVER 2 study showed an ACR20 response of 64% versus 33% with placebo at week 24 in TNF inhibitor-experienced patients.[17] Risankizumab also showed similar responses in the KEEPsAKE-1 and 2 trials. In in biologic naïve patients, ACR20 at week 24 was 57.3% versus 33.5% with placebo, while in TNF inhibitor-naïve and -experienced patients, the response was 51.3% versus 26.5%.[18,19] Among all therapies, bimekizumab showed the most favourable results in clinical trials, with a number needed to treat (NNT) of 3–4 to achieve ACR50. Other IL-17 and IL-23 inhibitors showed broadly similar efficacy with comparable NNT values. Radiographic progression has been assessed in several trials of IL-17 and IL-23 inhibitors. In

the FUTURE 5 trial, radiographic progression was assessed as a key secondary outcome, comparing secukinumab at doses of 300 mg and 150 mg, with or without a loading dose. At week 24, mean changes from baseline in the van der Heijde-modified total Sharp score (vdH-mTSS) demonstrated significant inhibition of radiographic structural progression across all secukinumab groups compared to placebo: 0.08 (300 mg with loading dose; $p < 0.01$), 0.17 (150 mg with loading dose; $p < 0.05$), and –0.09 (150 mg without loading dose; $p < 0.05$), versus 0.50 for placebo.[8] This difference in radiographic progression persisted through the 2-year follow-up period.[20] Although radiographic progression was a prespecified aim in the AMVISON-1 trial of brodalumab, it could not be assessed due to the early termination of the trial.[12,13] In the phase 3 trial of bimekizumab for bDMARD-naïve patients (BE OPTIMAL), radiographic progression was assessed as a secondary outcome. At week 16, progression in the vdH-mTSS was lower in the bimekizumab arm compared to placebo (0.01 versus 0.31, $p<0.01$). However, radiographic assessments were not a prespecified outcome in the BE COMPLETE trial, which evaluated bimekizumab in bDMARD-experienced patients with PsA.[14,15]

In contrast, the DISCOVER-2 trial evaluating guselkumab did not show a significant difference in radiographic progression with every-8-week dosing compared to placebo at week 24, with mean changes in vdH-mTSS of 0.52 versus 0.95 with placebo, although long-term results have shown promise.[17,21] Similarly, the KEEPsAKE 1 trial of risankizumab failed to demonstrate a significant difference in radiographic progression at 24 weeks.[18,19] A network meta-analysis of randomized controlled trials indicated that ixekizumab and secukinumab 300 mg were associated with higher rates of radiographic non-progression compared to guselkumab.[22] Interestingly, a recent trial was designed to more robustly assess radiographic progression with guselkumab by enrolling patients at higher risk of radiographic damage, using an adequately powered design, long-term follow-up of 3 years, and centralized radiographic assessment.[23] Results from this study show that patients on guselkumab had significantly reduced radiographic progression compared to placebo at week 24, with least square mean changes in vdH-mTSS of 0.55 (4 weekly) versus 0.54 (8 weekly) versus 1.35 (placebo).[24]

Thus, both IL-17 and IL-23 inhibitors appear to slow radiographic progression through their anti-inflammatory effects, thereby offering protection against structural joint damage in PsA **(Table 1)**.

- **Enthesitis:** Resolution of enthesitis has typically been assessed as a secondary outcome in clinical trials of IL-17 and IL-23 inhibitors. Across studies, approximately 50% of patients achieved enthesitis resolution, with placebo-adjusted differences ranging from 15% to 25%. These outcomes were influenced by factors such as baseline patient characteristics and trial inclusion criteria **(Table 1)**.
- **Dactylitis:** Dactylitis resolution has been evaluated as a secondary outcome in trials of IL-17 and IL-23 inhibitors. Secukinumab and brodalumab demonstrated resolution in approximately 50–60% of patients, with placebo-adjusted differences of approximately 30–35% in the FUTURE and AMVISION trials, respectively. Ixekizumab showed higher efficacy, with resolution rates close to 80% and placebo-adjusted differences of approximately 55% in the SPIRIT trials. Bimekizumab also showed promising results, with 76% of patients achieving dactylitis resolution; however, the placebo-adjusted difference was lower (25%), likely due to high placebo response rates. In contrast, IL-23 inhibitors such as guselkumab and risankizumab showed 60–70% of patients achieving complete resolution of dactylitis, though the placebo-adjusted differences were more modest, ranging from 15–30%. Overall, the newer IL-17 and IL-23 inhibitors demonstrate comparable effectiveness in dactylitis resolution, though the magnitude of response varies across agents and trial designs **(Table 1)**.
- **Axial disease:** IL-17 inhibitors have demonstrated efficacy in axial PsA. In the MAXIMISE trial, secukinumab was significantly superior to placebo in achieving Assessment of Spondylarthritis International Society 20%/40% improvement criteria (ASAS20) responses at week 12. This clinical benefit was accompanied by meaningful reductions in Berlin spine and sacroiliac MRI scores, further supporting its anti-inflammatory effect in axial disease.[25] In contrast, data for ixekizumab are less robust. A post hoc analysis of the SPIRIT-P1 and SPIRIT-P2 trials suggested significant improvements in patients with PsA who reported axial pain beginning before age 45.[26] The effectiveness of brodalumab and

Trial (Drug, Dose)	Inclusion Criteria	Primary Outcome	Primary Result	Secondary Outcomes	PASI	Enthesitis Resolution	Dactylitis Resolution	Drug–Placebo Δ (%)	NNT (Primary)
FUTURE 1 **IV secukinumab, 150 mg and 75 mg**[48]	Active PsA, TNFi naïve and experienced	ACR20, 24 W	50% (150 mg) vs. 17.3% (PBO)	vDH-mTSS mean change: 0.13 (150 mg) vs. 0.57 (PBO)	PASI 75: 61.1% (150 mg) vs. 8.3% (PBO)	47.5% (pooled) vs. 12.8% (PBO)	52.4% (pooled) vs. 15.5% (PBO)	32.7%	~3
FUTURE 2 **SC secukinumab, 300 mg, 150 mg and 75 mg**[7]	Active PsA, TNFi naïve and experienced	ACR20, 24 W	54% (300 mg) vs. 15% (PBO)	ACR50: 35% (300 mg) vs. 7% (PBO)	PASI 75: 63% (300 mg) vs. 16% (PBO)	40% (pooled) vs. 22% (PBO)	47% (pooled) vs. 15% (PBO)	39%	~3
FUTURE 3 **SC secukinumab, autoinjector, 300 mg and 150 mg**[6]	Active PsA, TNFi naïve and experienced	ACR20, 24 W	48.2% (300 mg) vs. 16.1% (PBO)	ACR50: 34.5% (300 mg) vs. 8.8% (PBO)	PASI 75: 46.8% (300 mg) vs. 10.2% (PBO)	39.8% (300 mg) vs. 15.3% (PBO)	47.8% (300 mg) vs. 13.9% (PBO)	~32%	~3
FUTURE 4 **SC secukinumab, 150 mg with and without LD**[9]	Active PsA, TNFi naïve and experienced	ACR20, 16 W	41.2% (150 mg LD) vs. 18.4% (PBO)	ACR50: 22.8% (150 mg LD) vs. 6.1% (PBO)	PASI 75: 52.7% (150 mg LD) vs. 8.1% (PBO)	32.4% (150 mg LD) vs. 21.1% (PBO)	32.5% (150 mg LD) vs. 31.8% (PBO)	~23%	~5
FUTURE 5 **SC secukinumab, 300 mg LD, 150 mg LD, and 150 mg without LD**[8]	Active PsA, biologic naïve + experienced	ACR20, 16 W	ACR20: ~62.6% (300 mg LD) vs. 27.4% (PBO)	vDH-mTSS mean change: 0.08 (300 mg LD) vs. 0.5 (PBO) ACR50: 39.6% (300 mg LD) vs. 8.1 (PBO)	PASI 75: 70% (300 mg LD) vs. 12.3% (PBO)	55.7% (300 mg LD) vs. 35.4 (PBO)	65.9% (300 mg LD) vs. 32.3% (PBO)	~35% (300 mg LD)	~3 (300 mg LD)
SPIRIT-P1 **SC ixekizumab, 80 mg every 2 and 4 W**[10]	Active PsA, biologic naïve	ACR20, 24 W	57.9% (4W) vs. 30.2% (PBO)	ACR50: 40.2% (4W) vs. 15.1% (PBO) vDH-mTSS change: 0.17 (4W) vs 0.49 (PBO)	PASI 75: 71.2% (4W) vs. 10.4% (PBO)	42.6% (4W) vs. 19.3% (PBO)	79.5% (4W) vs. 25% (PBO)	31.9%	~3
SPIRIT-P2, SC ixekizumab, 80 mg every 2 and 4 W)[11]	Active PsA, biologic experienced	ACR20, 24 W	53% (4W) vs. 20% (PBO)	ACR50: 35% (4W) vs. 5%, ACR70: 14% (PBO)	PASI 75: 56% (4W) vs. 15% (PBO)	35% (4W) vs. 22% (PBO)	75% (4W) vs. 21% (PBO)	28.5%	~4
AMVISON-1 and -2 SC Brodalumab, 140 mg vs. 210 mg at 0 and 1 W, followed by every 2 W[13,49]	Active PsA, biologic naïve	ACR20, 16 W	45.8% (140 mg) vs. 47.9% (210 mg) vs. 20.09 (PBO)	ACR50: 24.8% (140 mg) vs. 26.1 (210 mg) vs. 7.2% (PBO)	PASI 75: 52.4% (140 mg) vs. 75.5% (210 mg) vs. 10.4% (PBO)	42.3% (140 mg) vs. 39.1% (210 mg) vs. 23.7% (PBO)	40.9% (140 mg) vs. 50.8% (210 mg) vs. 24.2% (PBO)	~25-27%	~4

Trial (Drug, Dose)	Inclusion Criteria	Primary Outcome	Primary Result	Secondary Outcomes	PASI	Enthesitis Resolution	Dactylitis Resolution	Drug–Placebo Δ (%)	NNT (Primary)
MAXIMISE SC secukinumab, 300 mg and 150 mg[25]	Active axial PsA with BASDAI ≥4	ASAS20, 12 W	63% (300 mg) vs. 66% (150 mg) vs. 31% (PBO)	ASAS40: 44% (300 mg) vs. 12% (PBO)	-	-	-	~30%	~3
DISCOVER-1 SC guselkumab 100 mg every 4 and 8 W[16]	Active PsA, biologic experienced	ACR20, 24 W	52% (8 W) vs. 22% (PBO)	ACR50: 30% (8 W) vs. 9% ACR70: 14%, PASI90: 52%	PASI 75: 76 (8W) vs. 14% (PBO)	40% (8 W) vs. 27% (PBO)	65% (8 W) vs. 49% (PBO)	37.0%	~3
DISCOVER-2 SC guselkumab 100 mg every 4 and 8 W[17]	Active PsA, biologic naïve	ACR20, 24 W	64% (8 W) vs. 33% (PBO)	ACR50: 33% (8 W) vs. 14% (PBO), VDH-mTSS mean change: 0.52 (8W) vs 0.95 (PBO)	PASI 75: 79% (8 W) vs. 23% (PBO)	50% (8 W) vs. 29% (PBO)	59% (8 W) vs. 42% (PBO)	31.0%	~3
KEEPsAKE-1 SC risankizumab 150 mg at 0, 4, and 16 W[18]	Active PsA, biologic naïve	ACR20, 24 W	57.3% vs. 33.5% (PBO)	ACR50: 33.4% vs. 11.3%, VDH-mTSS change: 0.23 vs. 0.32 (PBO)	PASI 90: 52.3% vs. 9.9% (PBO)	48.4% vs. 34.8% (PBO)	68.1% vs. 51% (PBO)	23.8%	~5
KEEPsAKE-2 SC risankizumab 150 mg at 0,4, and 16 W[19]	Active PsA, biologic naïve and experienced	ACR20, 24 W	51.3% vs. 26.5% (PBO)	ACR50: 26.3% vs. 9.3% (PBO)	PASI 90: 55% vs. 10.2% (PBO)	42.9% vs. 30.4% (PBO)	72.5% vs. 42.1% (PBO)	24.8%	~4
BE OPTIMAL SC bimekizumab, 160 mg every 4 W[14]	Active PsA, biologic naïve	ACR50, 16 W	44%vs. 10% (PBO)	ACR20: 62% vs. 24% (PBO) MDA: 45% vs. 13% (PBO) vdH-mTSS change: 0.01 vs. 0.31 (PBO)	PASI 90: 61% vs. 3% (PBO)	50% vs. 35% (PBO)	76% vs. 51% (PBO)	34.0%	~3
BE COMPLETE SC bimekizumab, 160 mg every 4 W[15]	Active PsA, biologic experienced	ACR50, 16 W	43% vs. 7%	ACR20: 67% vs. 16% MDA: 44% vs. 6%	PASI 90: 69% vs. 7%	-	-	28.0%	~4

Table 1. Summary of phase 3 trials evaluating IL-17 and IL-23 inhibitors in psoriatic arthritis; *courtesy of Pankti Mehta, MD and Vinod Chandran, MD, MBBS, DM, PhD, FRCPC*

Abbreviations: ACR20/50/70: American College of Rheumatology 20%/50%/70% improvement criteria; **ASAS20/40:** Assessment of SpondyloArthritis International Society 20%/40% improvement criteria; **axPsA:** Axial Psoriatic Arthritis; **BASDAI:** Bath Ankylosing Spondylitis Disease Activity Index; **Dactylitis Resolution:** Percentage of patients achieving complete resolution of dactylitis; **Δ (%):** Absolute difference between drug and placebo response rates; **Enthesitis Resolution:** Percentage of patients achieving complete resolution of enthesitis; **IL:** Interleukin; **IV:** Intravenous; **LD:** Loading Dose, **MDA:** Minimal Disease Activity, **MRI:** Magnetic Resonance, **vdH-mTSS:** Modified total Sharp score using van der Heijde method; **NNT:** Number Needed to Treat; **PASI 75/90:** Psoriasis Area and Severity Index indicating 75%/90% reduction in severity; **PBO:** Placebo; **PsA:** Psoriatic Arthritis; **SC:** Subcutaneous; **TNFi:** Tumour Necrosis Factor inhibitor; **W/wk(s):** Week / weeks

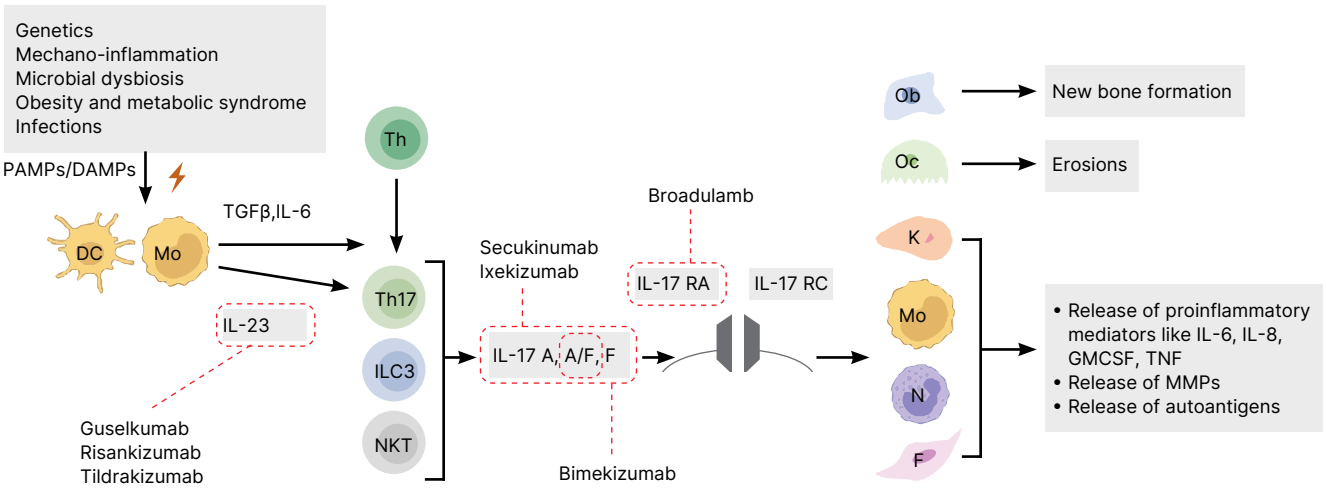

Figure 1. Therapeutic targets within the IL-23/IL-17 axis in psoriatic arthritis; *courtesy of Pankti Mehta, MD and Vinod Chandran, MD, MBBS, DM, PhD, FRCPC*

Abbreviations: PAMPs: pathogen associate d molecular patterns; **DAMPs:** damage associated molecular patterns; **Th:** T-helper; **ILC:** innate lymphoid cells; **NKT:** natural killer T cells; **DC:** dendritic cells; **Mo:** monocytes/macrophages; **Ob:** osteoblasts; **Oc:** osteoclasts; **K:** keratinocytes; **N:** neutrophils; **F:** fibroblasts

bimekizumab in axial PsA can be extrapolated from axial spondyloarthritis studies. Patients with axial spondyloarthritis showed significant improvements, with ASAS40 responses at week 16 in 43.8% with brodalumab versus 24.1% in the placebo group.[27] Similarly, bimekizumab demonstrated superiority over placebo in axial spondyloarthritis with an ASAS40 in both non-radiographic (47.7% versus 21.4%), and radiographic (44.8% versus 22.5%) axial spondyloarthritis. In contrast, data supporting the use of IL-23 inhibitors in axial PsA remains limited. A post hoc analysis of the DISCOVER-1 and DISCOVER-2 trials demonstrated improvements in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (−2.67 versus −1.35) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) (−1.4 versus −0.7) scores at week 52 among patients with imaging-confirmed axial involvement, compared to placebo.[28] Importantly, IL-23 inhibitors are not efficacious in treating axial spondyloarthritis.[29] The ongoing STAR study is designed to prospectively evaluate the efficacy of guselkumab in axial PsA using axial arthritis end points.[30]

Overall, while IL-23 inhibitors show promise, IL-17 inhibitors are supported by stronger and more direct evidence for use in axial PsA, particularly as demonstrated in the MAXIMISE trial.

- **Comparison of drugs for musculoskeletal domains:** There are no direct head-to-head trials comparing IL-17 and IL-23 inhibitors in PsA. However, post hoc analyses using matching-adjusted indirect comparisons have been conducted between bimekizumab and risankizumab, drawing on data from BE OPTIMAL and KEEPsAKE 1 for bDMARD-naïve patients, and BE COMPLETE and KEEPsAKE 2 for those with prior TNF inhibitor experience. In TNF inhibitor-naïve patients, bimekizumab had a significantly greater likelihood of ACR50 and ACR70 responses at week 52 than risankizumab, with odds ratios (95% confidence intervals [CI]) of 1.52 (1.11–2.09) and 1.80 (1.29–2.51), respectively. In the TNF inhibitor-experienced group, bimekizumab also demonstrated a significantly greater likelihood of response than risankizumab at week 52, with odds ratios (95% CI) of 3.05 (1.74–5.32) for ACR50, 3.69 (1.82–7.46) for ACR70, and 2.43 (1.37–4.32) for achieving minimal disease activity (MDA).[31] A recent network meta-analysis compared the efficacy of bimekizumab with other IL-17 and IL-23 inhibitors in PsA. Among bDMARD-naïve patients, bimekizumab demonstrated superior efficacy in achieving ACR50 response rates compared to IL-23 inhibitors, while showing comparable efficacy to IL-17A inhibitors such as secukinumab and ixekizumab. In contrast, among patients with prior TNF inhibitor exposure,

bimekizumab showed similar efficacy to IL-23 inhibitors and better efficacy compared with IL-17 inhibitors, suggesting consistent effectiveness across treatment-experienced populations.[32]

Thus, while most IL-17 and IL-23 inhibitors offer substantial benefit for inflammatory arthritis, bimekizumab may be the most effective based on available comparative efficacy data.

Inflammatory Bowel Disease

Although IL-17 inhibitors have been associated with a risk of new-onset or worsening of IBD, such events are relatively rare. As a result, they are generally avoided in patients with a personal history or elevated risk of IBD.[33] There is a mechanistic basis for the occurrence of IBD, including disruption in the gut mucosal barrier, interference with the regulatory role of IL-17A via IL-24, and routing of inflammation through the TNF-like ligand 1A pathway.[34] In contrast, IL-23 inhibitors have demonstrated efficacy in treating both Crohn's disease and ulcerative colitis, making them a more suitable choice for PsA patients who either have or are at high risk of developing IBD.[35]

Psoriasis

Both IL-17 and IL-23 inhibitors are highly effective for treating moderate-to-severe psoriasis, leading to significant reductions in the Psoriasis Area and Severity Index (PASI) and improved skin clearance.[36-38] While both classes achieve high efficacy, IL-17 inhibitors tend to produce more rapid skin improvement, whereas IL-23 inhibitors offer sustained long-term benefits with infrequent dosing.[39,40]

Interestingly, observational registry-based data suggest that IL-23 inhibitors may reduce the risk of developing incident PsA over a 2.4 year period, with a hazard ratio (HR) of 0.41 (95% CI, 0.17–0.95) compared to TNF inhibitors. In contrast, no significant differences were observed between IL-17 inhibitors and TNF inhibitors in this regard.[41] Another study involving 622 patients with psoriasis

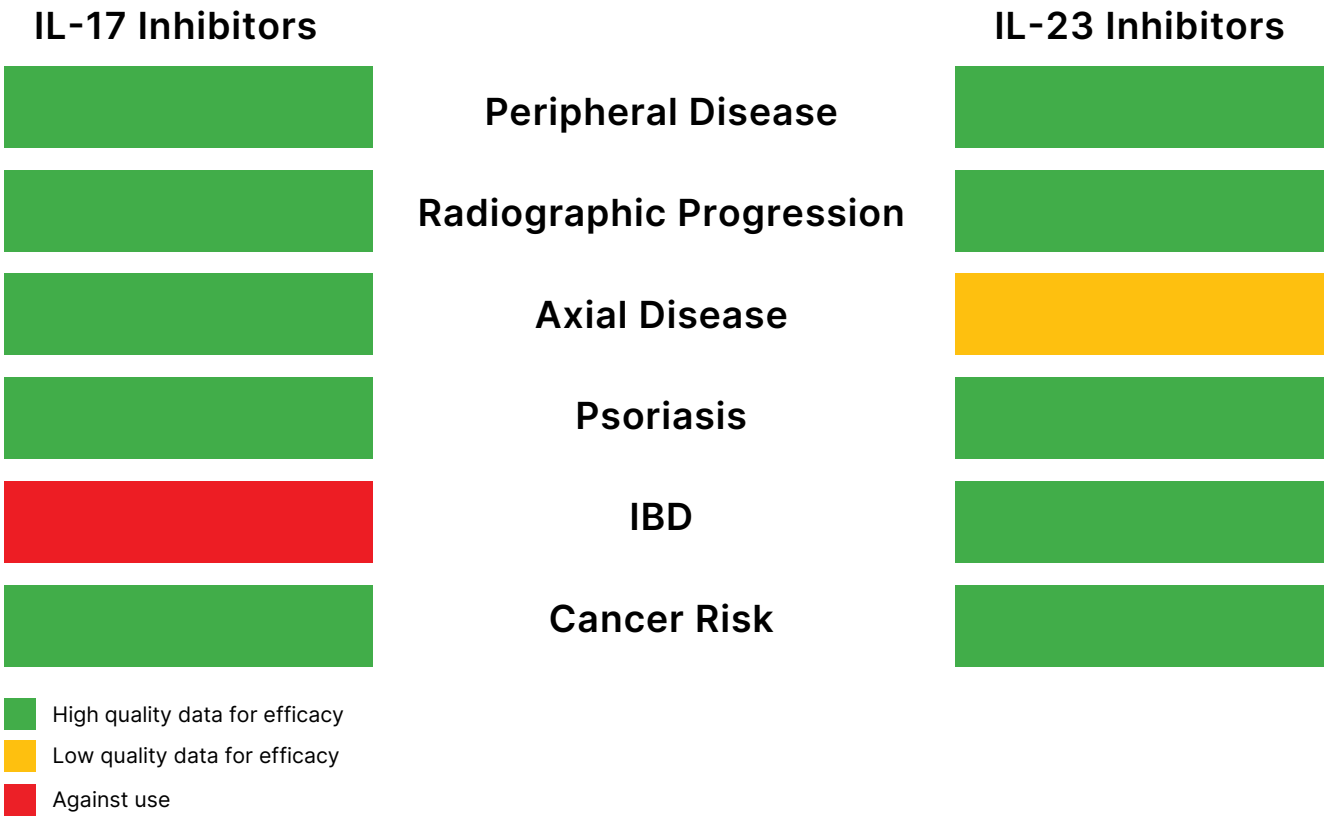

Figure 2. Summary of the quality of evidence for IL-17 and IL-23 inhibitors across various domains of psoriatic arthritis; *courtesy of Pankti Mehta, MD and Vinod Chandran, MD, MBBS, DM, PhD, FRCPC*

Abbreviations: IL: interleukin; **IBD:** inflammatory bowel disease

found that both IL-17 inhibitors (HR 0.63, 95% CI, 0.38–1.05) and IL-23 inhibitors (HR 0.57, 95% CI, 0.34–0.96) were associated with a reduced risk of PsA compared to TNF inhibitors.[42] These findings suggest a potential role for IL-23 inhibitors in PsA prevention, although further prospective studies are needed.

Safety

Clinical trials, registries, and real-world cohorts consistently show that both IL-17 and IL-23 inhibitors have favourable safety profiles,[43,44] with no significant increase in serious infections. However, IL-23 inhibitors appear to have a slightly better safety profile, largely due to a lower incidence of non-serious Candida infections[43,44] compared to IL-17 inhibitors. Common adverse events reported across both classes include nasopharyngitis, upper respiratory tract infections, injection site reactions, and headaches. Neither IL-17 nor IL-23 inhibitors have been associated with an increased risk of malignancy.[45,46] On the contrary, emerging data suggest a reduced risk of cancer compared to biologic naïve patients.[47] Among IL-17 inhibitors, brodalumab was initially associated with suicidal ideation in early trials, though subsequent investigations did not establish a causal link.[12]

In conclusion, both IL-17 and IL-23 inhibitors are effective and well-tolerated treatment options for treating PsD, each offering distinct advantages based on clinical phenotype and comorbidities. For psoriasis, both classes demonstrate comparable efficacy. IL-17 inhibitors are generally preferred for axial involvement due to stronger evidence of benefit, whereas IL-23 inhibitors may be considered in patients with coexisting IBD, given their favourable gut-specific anti-inflammatory profile. In peripheral arthritis, IL-17 inhibitors, particularly bimekizumab, may offer superior efficacy with a more rapid onset of action and potential inhibition of radiographic progression, though head-to-head trials are warranted. IL-23 inhibitors are especially suitable for patients with concurrent IBD. Preliminary evidence also suggests that IL-23 inhibitors may prevent incident PsA in patients with psoriasis, although further research is needed. Overall, both drug classes exhibit favourable safety profiles, with IL-23 inhibitors associated with a slightly lower risk of mucocutaneous infections **(Figure 2)**.

Looking ahead, future research should focus on direct head-to-head comparisons of IL-17 and IL-23 inhibitors to inform treatment strategies. Additional studies are also needed to validate the role of IL-23 inhibitors in axial PsA and preventing PsA among patients with psoriasis. Long-term safety monitoring, exploration of combination strategies, and the integration of biomarkers for individualized treatment will be key to optimizing care in this heterogeneous disease.

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