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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

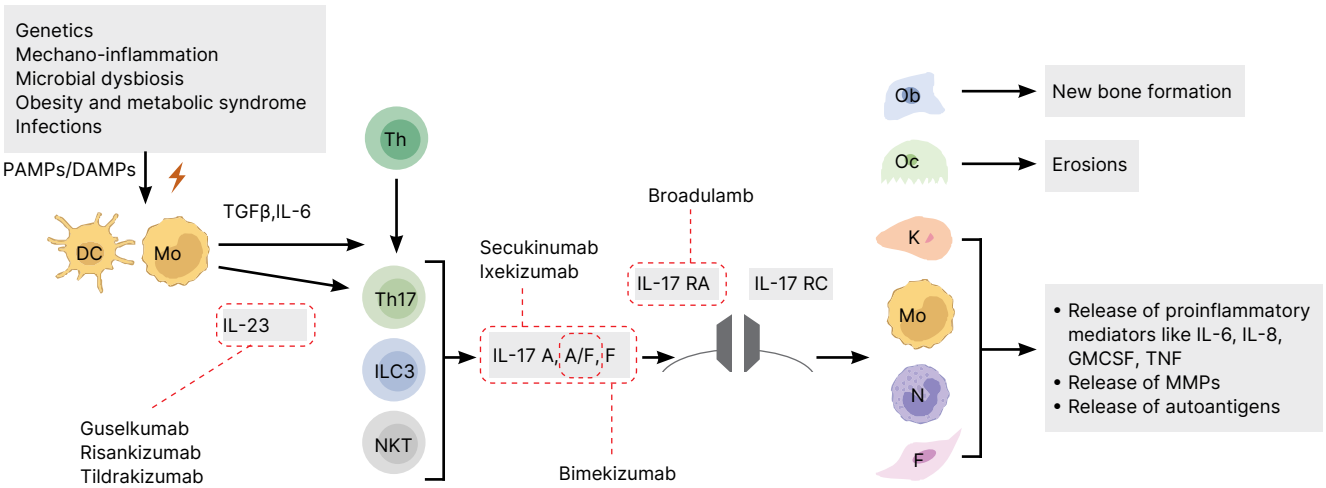

Figure 1. Therapeutic targets within the IL-23/IL-17 axis in psoriatic arthritis; *courtesy of Pankti Mehta, MD and Vinod Chandran, MD, MBBS, DM, PhD, FRCPC*

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

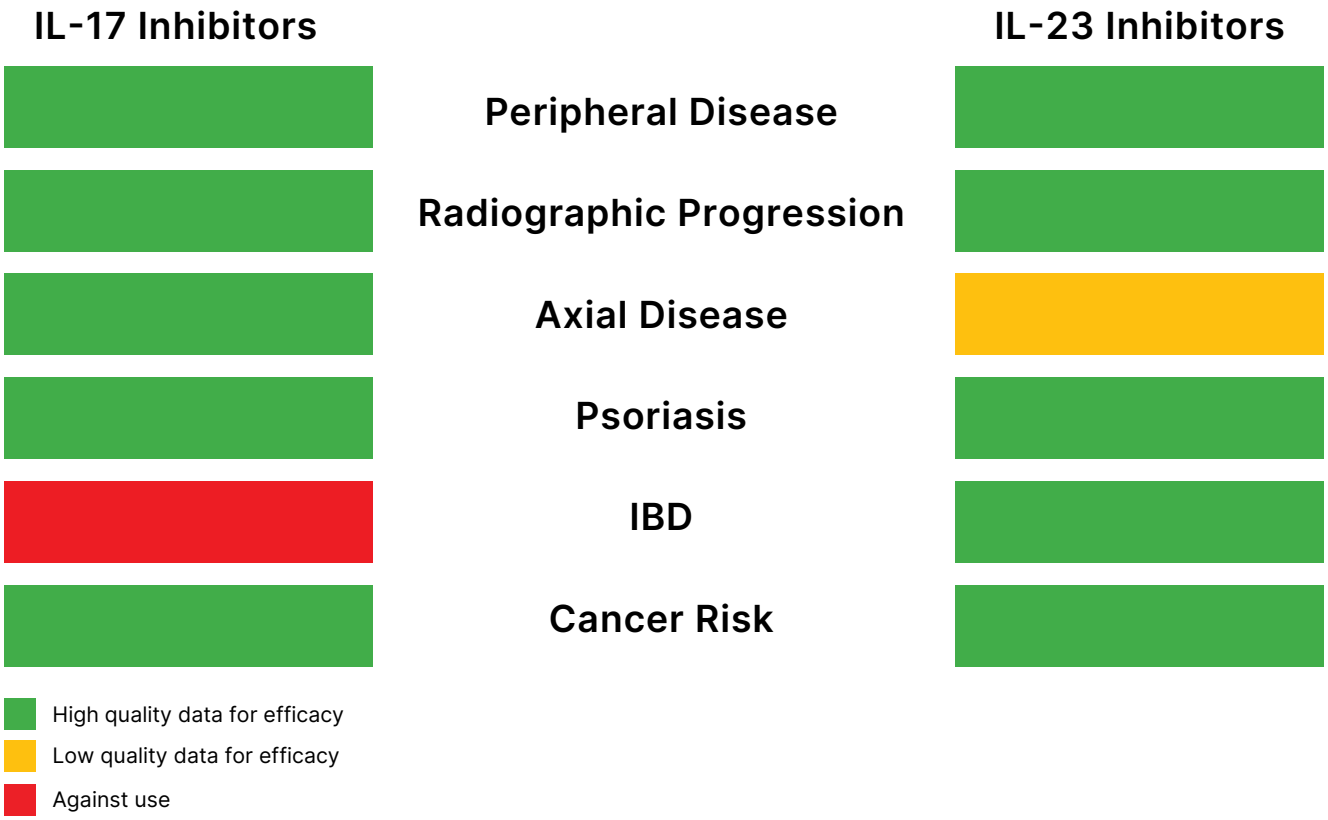

Figure 2. Summary of the quality of evidence for IL-17 and IL-23 inhibitors across various domains of psoriatic arthritis; *courtesy of Pankti Mehta, MD and Vinod Chandran, MD, MBBS, DM, PhD, FRCPC*

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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Can We Prevent Psoriatic Arthritis?

Alexandra Kobza, MD, FRCPC

Abstract

Psoriatic arthritis (PsA) is a chronic, inflammatory musculoskeletal disease that often develops in individuals with psoriasis (PsO), typically following an average latency period of 7 years. Without treatment, PsA can lead to irreversible joint damage, functional impairment, and a range of comorbidities. Despite therapeutic advances, only a minority of patients achieve sustained remission, highlighting the need for new approaches, including disease prevention and early interception. This review explores the emerging concept of PsA prevention in individuals with psoriasis, by addressing modifiable risk factors—such as severe skin disease, nail involvement, and obesity—and predictors such as arthralgias and asymptomatic abnormalities on musculoskeletal ultrasound. Notably, PsO patients represent a unique preventive opportunity in rheumatology, as many treatments address both PsO and PsA, potentially minimizing additional therapeutic risks.

A recently proposed framework by the European Alliance of Associations for Rheumatology (EULAR) outlines three stages of progression from PsO to PsA, ranging from individuals 'at higher risk', to those with 'subclinical PsA', and finally to those with 'clinical PsA'. Findings from observational studies suggest that treatment of modifiable risk factors may reduce PsA incidence, though prospective data remain limited. Subclinical inflammation detected on imaging and the presence of arthralgia may identify individuals at imminent risk who could benefit from escalation of therapy. Nonetheless, further refinement of this population is necessary to avoid overtreatment. Ongoing clinical trials are expected to help clarify whether early intervention can truly intercept PsA and alter its natural history. Ultimately, success in PsA prevention will require multidisciplinary collaboration, refinement of risk stratification, and thoughtful integration of these screening strategies into clinical practice.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease that shares both genetic and clinical features with other forms of spondyloarthritis. While it is commonly characterized by psoriasis (PsO) and arthritis, PsA encompasses other disease domains, such as enthesitis, axial disease, uveitis, inflammatory bowel disease, dactylitis and nail disease. PsA is also associated with numerous comorbidities, including cardiovascular disease, obesity, type

2 diabetes, hypertension, metabolic syndrome, fatty liver disease, osteoporosis, fibromyalgia, depression, and anxiety.[1] Left untreated, PsA can result in irreversible structural damage, functional impairment, and reduced quantity and quality of life—highlighting the need for timely and effective therapy.[2]

Despite available treatments, only approximately 30% of patients with PsA achieve remission with any given biologic therapy, making disease prevention an increasingly appealing concept.[2] This idea of disease prevention is not new to rheumatology, with several research groups across various rheumatologic diseases working to identify at-risk populations that may benefit from intervention prior to the onset of irreversible disease.[3] However, any early intervention must balance the potential benefits against both the risks and costs of treating individuals who may never develop the disease.

PsA presents a unique opportunity for interception, as approximately 70% of cases are preceded by PsO, with PsA developing on average 7 years after the onset of PsO.[4] This latency period offers a window for risk stratification—as only 30% of patients with PsO will develop PsA—and early intervention. Furthermore, PsO and PsA share common immunopathological pathways and many of the same therapies, potentially reducing incremental risks from early treatment. Therefore, carefully selected interventions could not only treat PsO but also prevent PsA and its associated complications in patients at high-risk for PsA development.[2] This review outlines current progress toward this goal.

Developing a Framework for Pre-Clinical Psoriatic Arthritis

Identifying patients at high-risk of developing PsA begins with understanding its risk factors. Established risk factors include obesity, severe psoriasis, nail involvement, and a family history of PsA in a first-degree relative.[4-6] Other potential risk factors include infections, mechanical stress, and depression, though data are mixed.[7]

Imaging of the synovio-entheseal complex may offer more sensitivity than clinical examination for detecting early musculoskeletal inflammation. Studies have shown that asymptomatic synovitis and enthesopathy occur more frequently in PsO patients compared to controls.[8,9] At the same time, the presence of such abnormalities in over 50% of PsO patients—and even in some healthy controls—on musculoskeletal ultrasound raises concerns about the lack of specificity with isolated imaging changes.[9]

Arthralgias, regardless of inflammatory pattern, also appear to be a predictor of imminent PsA. One study found that PsO patients with arthralgias had markedly higher PsA progression at 12 and 36 months (9.4% and 22.7%, respectively), compared to the annual incidence of 0.3 3.7% reported in the literature for all-comers with psoriasis.[10]

To support coordinated research efforts, three working groups have proposed frameworks to define the progression from PsO to PsA, integrating these risk factors and predictive markers.[4-6] Most recently, in 2023, the European Alliance of Associations for Rheumatology (EULAR) task force proposed a three-stage model describing the PsO-PsA continuum.[6]

- **Stage 1: At Higher Risk:** PsO patients with risk factors such as severe skin disease, nail involvement or high body mass index (BMI)
- **Stage 2: Subclinical PsA:** PsO patients with arthralgia and/or imaging evidence of synovio-entheseal inflammation without clinical synovitis
- **Stage 3: Clinical PsA:** Patients with PsO and clinical synovitis

While some task force members argue that patients with arthralgia and imaging evidence of synovio-entheseal inflammation could already be considered to have clinical PsA, EULAR consensus favours reserving the 'clinical PsA' label for those with definitive physical examination findings of synovitis, given the limited specificity of imaging as discussed previously. By designating patients with arthralgia and imaging findings as 'subclinical PsA', the framework encourages targeted research on this high-risk group.[6]

The EULAR model also outlines a typical timeline for disease progression: Stage 1 on average spans 7–12 years, Stage 2 usually precedes clinical PsA by 1–3 years, and Stage 3 marks disease onset. Risk factors are temporally stratified, with obesity, severe psoriasis, and nail disease being long-term risk factors (Stage 1), while arthralgia and musculoskeletal imaging abnormalities are short term risk factors (Stage 2). EULAR recommends that "prevention" applies to interventions targeting Stage 1, and "interception" refers to strategies aimed at Stage 2.[6]

The framework also shows the timeline required for prospective studies aiming to use PsA incidence as the outcome. For patients in Stage 2, the authors suggest that changes in arthralgias or

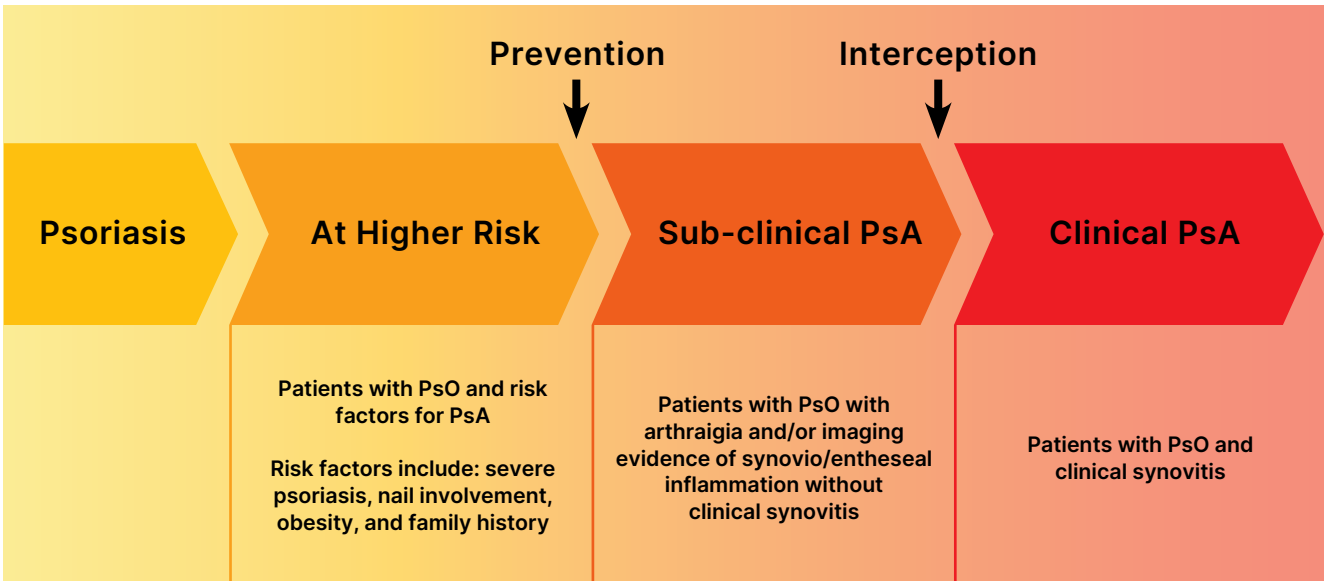

Figure 1. EULAR proposed phases of transition from PsO to PsA, adapted from Zabotti et al.[6]

Abbreviations: PsO: psoriasis; **PsA:** psoriatic arthritis

resolution of imaging abnormalities could serve as surrogate outcomes in trials evaluating PsA interception.[6] The EULAR framework is presented in **Figure 1**.

Shared Immunopathology of Psoriasis and Psoriatic Arthritis

A key rationale for focusing on PsA interception in PsO patients is the shared immunopathology between skin and joint disease as illustrated in **Figure 2**. Many therapies are effective in treating both PsO and PsA, suggesting that preventive treatment may pose minimal additional risks beyond treating PsO itself.[1] This is in contrast with strategies in other autoimmune diseases, where prevention often involves treating otherwise healthy individuals.

Both the skin and enthesis share similar microanatomical features, with the epidermis and fibrocartilage zones being relatively avascular and susceptible to Koebnerisation—a phenomenon whereby mechanical injury can trigger disease onset. Both sites are populated by similar innate immune cells—including resident macrophages, neutrophils, and plasmacytoid dendritic cells—as well as intermediate lymphocytes, such as group 3 innate lymphoid cells, γδ T cells, and mucosal-associated invariant T (MAIT) cells. Interleukin (IL)-23 released by innate myeloid cells can activate the intermediate lymphocytes, leading to the release of IL-17A, tumour necrosis factor (TNF), and other pro-inflammatory cytokines that drive skin and joint inflammation, bone erosion, and pathological bone formation. In addition, conventional T cells, including CD4+ and CD8+ T cells—particularly tissue-resident memory CD8+ T cells—are found at both sites.[12] These shared immune pathways support the feasibility of targeting this pathway to intercept disease before clinical joint symptoms arise.

Evidence to Date

Several studies to date have explored the prospect of PsA prevention and interception. Beginning with the risk factor of obesity, a prospective study of 90,189 individuals with incident psoriasis by Green et al found that linear reductions in BMI over a 10-year period were associated with a decreased risk of developing PsA, compared to those who maintained a constant BMI from the same baseline. This finding suggests that weight management may help prevent the onset of PsA.[13] Bariatric surgery has also been associated with lower PsA incidence: a Danish cohort study found gastric bypass (but not gastric banding) reduced PsA risk (hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.12–0.71). The reason for these discrepant results between gastric bypass and banding remains unclear particularly as weight change data were not available in the study.[14] To date no studies have evaluated the effect of weight loss medications,

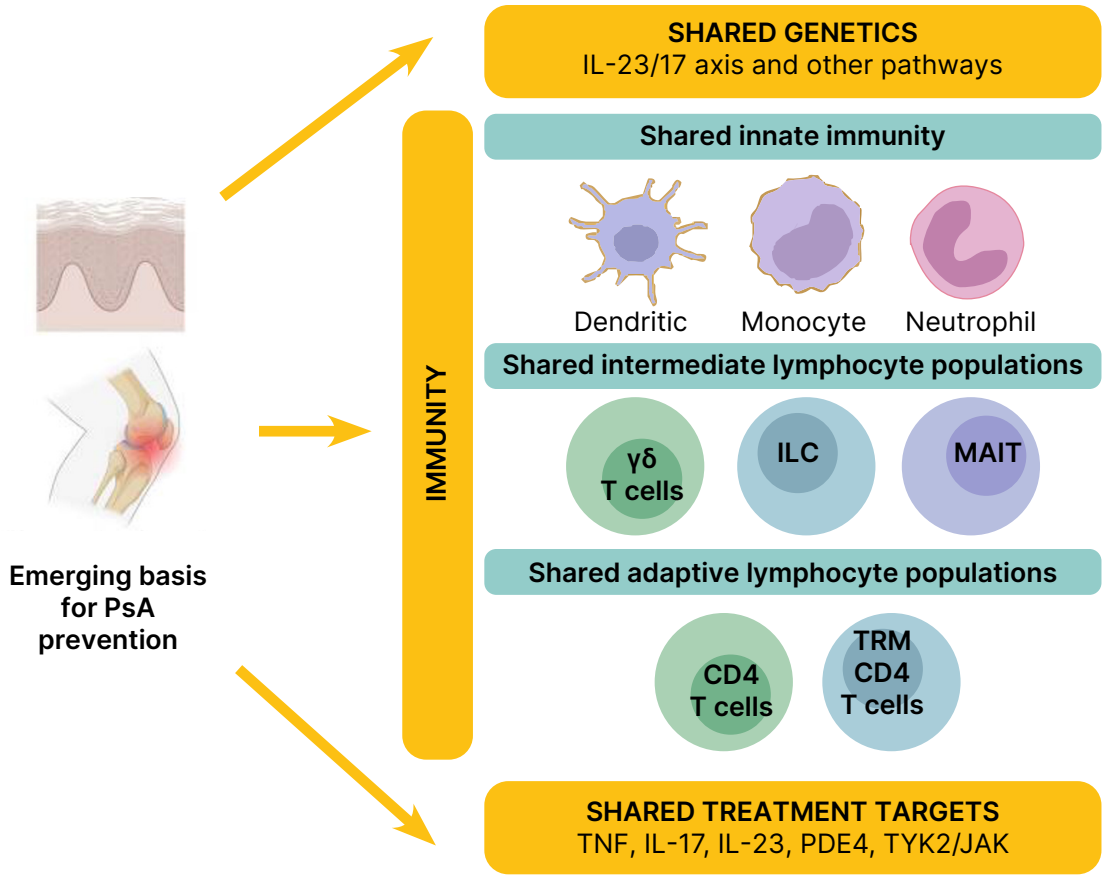

Figure 2. Emerging basis for PsA prevention based on therapeutic management of psoriasis; reproduced from López-Medina et al., Rheumatology (Oxford), 2024,[11] under the terms of the Creative Commons Attribution Licence (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/

Abbreviations: ILC: innate lymphoid cells; **JAK:** Janus kinase; **MAIT:** mucosal-associated invariant T cell; **PDE4:** phosphodiesterase-4; **PsA:** psoriatic arthritis; **TRM:** tissue-resident memory T cell; **TYK2:** tyrosine kinase 2.

such as glucagon-like peptide-1 (GLP-1) receptor agonists for PsA prevention.

Several retrospective studies have assessed the impact of PsO therapies on PsA incidence. Gisondi et al. looked at 464 patients with moderate-to-severe PsO and found lower PsA in patients treated with biologic disease-modifying antirheumatic drugs (DMARDs) versus phototherapy (HR 0.53, 95% CI 0.30–0.94).[15] Conversely, Meer et al. reported higher PsA risk with biologics versus conventional DMARDs or phototherapy in a larger cohort of 193,709 individuals. However, the authors cautioned that these results may be due to confounding by indication and protopathic bias (i.e., treating early PsA symptoms before a formal diagnosis has been made).[16] In another study of nearly 20,000 patients, apremilast has shown lower PsA risk than methotrexate (HR 0.85, 95% CI 0.79–0.91).[17] Additionally, IL-23 and IL-12/23 inhibitors have been associated with lower PsA incidence compared to TNF inhibitors in two studies, while IL-17 inhibitors showed no significant difference in risk compared to TNF inhibitors.[18-19]

While many of these results are biologically plausible, they should be interpreted with caution. Observational studies are prone to confounding by indication, which occurs when treatments are prescribed based on disease severity or early symptoms—resulting in systematic differences between treatment groups that may influence outcomes independent of the treatment itself. These studies are also subject to selection bias (e.g., patients with more severe PsO being more likely to receive biologics), making the results not generalizable for all patients with psoriasis. Additionally, protopathic bias, as described

above, may occur when treatment is initiated for early, undiagnosed manifestations of PsA.[20] Nevertheless, these studies generate hypotheses for prospective trials.

Notably, most studies focus on managing patients with moderate-to-severe PsO, which itself is a major risk factor for PsA (Stage 1 of the EULAR framework). However, more research is needed for patients with subclinical PsA (Stage 2). One such study by Savage et al. evaluated 23 patients with PsO and ultrasound-confirmed subclinical enthesitis who were treated with ustekinumab for 52 weeks. The study reported reductions in ultrasound inflammation scores of 42.2% at week 24 and 47.5% at week 42, suggesting a potential benefit.[21] Additionally, a randomized placebo-controlled trial is currently underway to assess the effects of guselkumab in PsO patients with musculoskeletal ultrasound abnormalities with outcomes focused on changes in imaging and PsA incidence.[22]

Remaining Gaps

These interesting and encouraging results have raised new questions. Is it possible that some interventions could be effective in decreasing PsA incidence for those 'at higher risk of PsA' (stage 1) while others may be more suitable to implement for those with 'subclinical PsA' (stage 2). To achieve this level of precision, additional prospective studies are required to determine which therapies or strategies are the most effective at each stage. Given that not all patients with arthralgias and/or musculoskeletal imaging abnormalities progress to PsA, more precise tools are needed to define the group of patients most suitable for interception. Furthermore, the impact of PsA prevention on associated metabolic and psychological comorbidities remains unclear, as do the risk-benefit profile and cost-effectiveness of such strategies.

The feasibility and efficacy of screening all PsO patients with musculoskeletal ultrasound also requires further evaluation. Furthermore, since 30% of PsA patients do not have preceding PsO, the challenge remains as to how to prevent or intercept disease in this group. Ultimately, achieving success in PsA prevention and interception will require a substantial expansion of dedicated research and coordinated efforts among rheumatologists, dermatologists, and primary care physicians.

Conclusion

Preventing and intercepting PsA is becoming an increasingly feasible and compelling goal, particularly among individuals with psoriasis who exhibit well-established risk factors. The shared immunopathology between psoriasis and PsA, coupled with a defined pre-clinical window, provides strong justification for early, targeted intervention before the onset of clinical synovitis. Currently, there is good clinical rationale and evidence to treat risk factors—obesity, severe psoriasis, nail disease—based on existing guidelines, as they also have the potential to prevent the development of PsA.

However, despite growing momentum around PsA prevention and interception, caution is still warranted when considering escalation of therapy in psoriasis patients presenting with arthralgias and/or subclinical musculoskeletal abnormalities on imaging. Further stratification of this population is necessary to better identify those at highest risk of PsA development and to avoid potential overtreatment. The recently proposed EULAR framework offers a useful structure for studying this group and designing future trials. Observational insights can now be tested in prospective, controlled settings to evaluate whether PsA—and its associated comorbidities—can be effectively intercepted. As evidence continues to evolve, the thoughtful integration of preventive strategies into clinical practice holds significant promise for reducing the long-term burden of PsA before irreversible joint damage and comorbidities arise.

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Idiopathic Inflammatory Myopathy-Associated Cancer: A Review of Risk Factors and Screening Recommendations

Eugene Krustev, MD

Abstract

Idiopathic inflammatory myopathies (IIMs) are a group of rare autoimmune diseases that are characterized by autoimmune myositis. However, systemic extramuscular manifestations are frequently observed. IIMs have been associated with cancer, and given the increased frequency of co-incident cancers in IIM, malignancy screening in newly diagnosed IIM patients is an important consideration. That being said, cancer risk varies across IIM subtypes, antibody specificities, and with clinicodemographic factors. As such, cancer screening should be tailored using a risk stratification approach. This review discusses the evidence regarding cancer risk in IIM, as well as recently-published guidelines for cancer screening in IIM.

Introduction

Idiopathic inflammatory myopathies (IIM) represent a heterogeneous group of autoimmune diseases characterized by the presence of autoimmune myositis. They can be divided into six subtypes: dermatomyositis (DM), polymyositis (PM), antisynthetase syndrome (ASyS), immune-mediated necrotizing myopathy (IMNM), overlap myositis syndromes (OM), and inclusion body myositis (IBM).[1] It is well recognized that IIM patients have an increased risk of concurrent malignancies, many of which are diagnosed in the three years before or after the onset of IIM symptoms.[2] The first documented description of IIM-associated cancer was published by Dr. Stertz in 1916.[3] Since then, a significant body of research has been dedicated to this association. Several factors influence cancer risk in IIM, including IIM disease subtype, antibody specificity, clinical manifestations, and demographic factors.

Given the numerous factors that influence cancer risk in IIM, risk assessment is based on expert opinion.[4] At present, we do not have the tools to assign highly specific risk scores to patients. Based on the presence of certain risk factors, patients can be stratified into three groups: those with the highest risk of malignancy

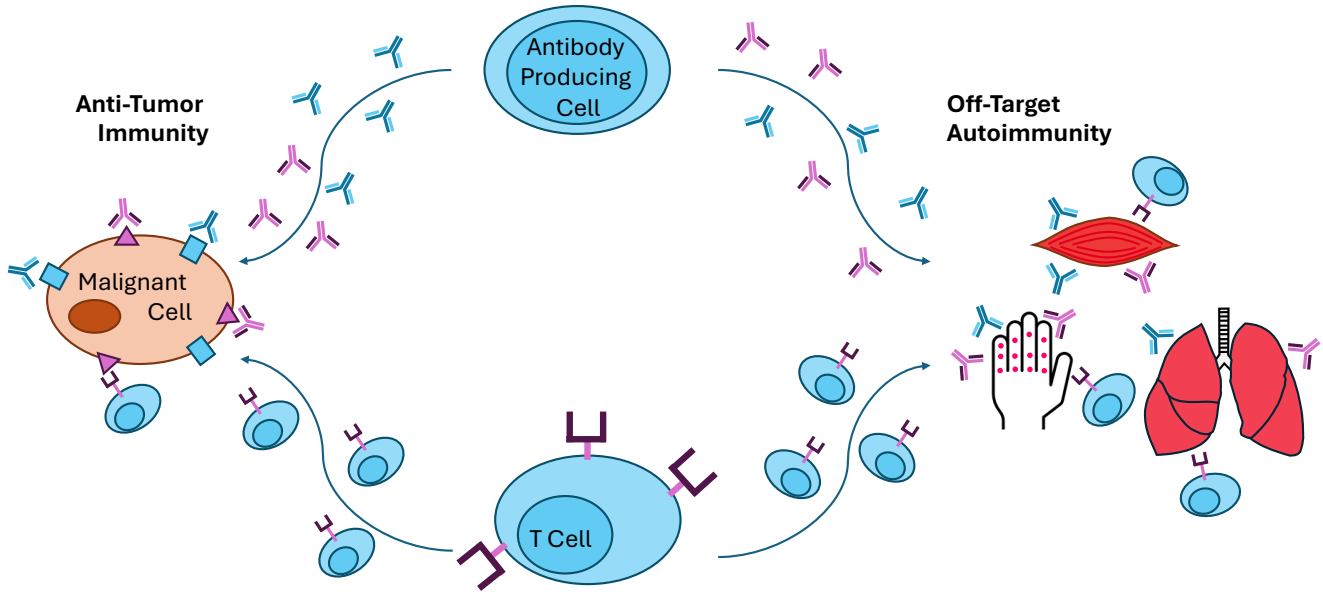

Figure 1. Anti-tumour and off-target immune responses in idiopathic inflammatory myopathy; *courtesy of Eugene Krustev, MD*

It has been postulated that in certain IIM subtypes, the initial immunologic trigger starts from an endogenous immune response directed toward cancer antigens. These antigens, which can be expressed either in a mutated form or over-expressed by malignant cells, induce an immune response. This immune response can then spread to off-target organs and result in the development of autoimmune myositis or other organ manifestations. The targeting of healthy cells can occur either from expression of the target antigen or other antigens with shared epitopes.

(high risk), those with a moderate but still notable risk (intermediate risk), and those with the lowest likelihood of malignancy (low risk).[4] Additionally, the types of cancers associated with IIM vary significantly based on factors such as sex, age, ethnicity, and geographic location. Therefore, when discussing malignancies linked to IIM, we will consider the full spectrum of potential cancer types, including both solid organ and hematologic cancers, as well as all possible cancer stages. These variables influence cancer risk in IIM, allowing for both risk stratification and a personalized approach to cancer screening in individuals with IIM.

Pathobiology of Idiopathic Inflammatory Myopathy-Associated Cancer

The frequent co-incidence of cancer within three years before or after IIM onset suggests a paraneoplastic phenomenon. Recent evidence suggests that in some patients IIM develops as a secondary effect of an endogenous anti-tumour immune response, in which off-target autoimmunity is directed toward muscles and other organs[5] **(Figure 1)**. In patients with IIM-associated cancer who test positive for anti-transcription intermediary factor 1-γ (anti-TIF1-γ), their tumours often exhibit upregulated expression of the TIF1-γ antigen and may harbour a mutated form of TIF1-γ.[6] This provides preliminary evidence that the antibodies found in patients with IIM-associated cancer may initially arise in response to mutated neoantigens or upregulated tumour antigens. It is likely that the development of IIM then requires a 'second hit', which then results in the development of IIM. This 'second hit' could be an underlying genetic defect that impairs immune system checkpoints or an environmental trigger that reactivates an aberrant immune response. In some patients, this anti-tumour response is effective in eliminating malignant cells, resulting in the presentation of IIM without cancer. On the other hand, in others, the anti-tumour response may fail to clear the cancer, leading to the co-occurrence of both cancer and IIM. This hypothesis helps explain why cancer is frequently associated with IIM, as well as why some patients present without an identifiable malignancy.[7] Future research is needed to help us better

understand how anti-tumour responses result in paraneoplastic autoimmune phenomena, including IIM.

Cancer Risk by Idiopathic Inflammatory Myopathy Subtype and Antibody Specificity

Dermatomyositis

DM is characterized by autoimmune myositis accompanied by characteristic skin rashes and is associated with several antibodies, including anti-Mi-2, anti-nuclear matrix protein 2 (anti-NXP2), anti-TIF1-ɣ, anti-melanoma differentiation-associated protein 5 (anti-MDA5), and anti-small ubiquitin-like modifier activating enzyme (anti-SAE). Among IIMs, DM confers the highest malignancy risk. A meta-analysis, which included 69 studies with 19,135 patients, demonstrated that DM patients had a significantly elevated cancer risk compared to those with non-DM IIM subtypes (relative risk [RR] 2.21; 95% confidence interval [CI] 1.78, 2.77).[2] The DM-associated antibody anti-TIF1-γ is associated with the greatest malignancy risk in IIM and is present in almost half of IIM-associated cancers.[8-10] While earlier studies suggested a strong association between anti-NXP2 and malignancy,[11] more recent evidence suggests that this association is weaker than previously thought.[2,12] The association between anti-Mi-2 and anti-SAE antibodies and malignancy is mixed, though at least one study has shown an association.[8] In contrast, anti-MDA5 does not appear to confer an increased risk of malignancy compared to other IIM subtypes[13] or the general population.[8] As such, DM patients, especially those who are anti-TIF1-γ positive, require the most rigorous screening for co-incident malignancies.

The most common cancers that are found in DM patients vary based on age, sex, ethnicity, and country of residence. In an American cohort, breast and ovarian cancers were the most commonly observed malignancies among DM patients, specifically in those who tested positive for anti-TIF1-γ antibodies.[8] A meta-analysis of 14 studies conducted across Asian countries identified nasopharyngeal and lung cancers as the most common malignancies in this population.[14] In a cohort of patients from Europe, ovarian, lung, pancreatic, stomach, and colorectal cancers, as well as lymphomas, were the most commonly seen malignancies in DM patients.[15] It is important to note, however, that while these malignancies are frequently reported in specific cohorts, many other cancer-types have been described in DM patients.

Clinically Amyopathic Dermatomyositis

Some DM patients can present with active skin disease but little to no muscle disease, a subtype referred to as clinically amyopathic dermatomyositis (CADM). A meta-analysis reported that patients with CADM had a decreased risk of malignancy compared to patients across other IIM subtypes (RR 0.44; 95% CI 0.20, 0.97).[2] However, previous studies have shown a cancer risk comparable to that of DM.[16] Given the rarity of CADM and variability in its definition across studies, future research is needed to further clarify the actual cancer risk for those with CADM.

Antisynthetase Syndrome

ASyS is characterized by a constellation of potential manifestations including autoimmune myositis, interstitial lung disease (ILD), inflammatory arthritis, hyperkeratotic skin changes and rashes, fever, and Raynaud's phenomenon. That being said, not all patients exhibit the full complement of manifestations, and partial presentations are common. The defining autoantibodies in ASyS are directed against various tRNA synthetases. Most studies evaluating cancer risk in ASyS have involved smaller cohorts, which limits comparisons to the general population. One study reported that cancer risk in ASyS was comparable to that of the general population,[8] while a meta-analysis reported a trend toward reduced malignancy risk compared to other IIM subtypes (RR 0.28; 95% CI 0.00, 6554.79).[2] Furthermore, several clinical signs that are associated with ASyS confer a reduced cancer risk, which will be discussed below. Collectively, these results suggest that ASyS is generally not associated with cancer.[2]

Immune-mediated Necrotizing Myopathy

IMNM is characterized by significant muscle fiber necrosis observed on biopsy, along with significant elevations in muscle enzymes and muscle weakness.[17] The autoantibodies most frequently associated with IMNM include anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) and anti-signal recognition particle (anti-SRP). Studies looking at cancer risk associated with IMNM, especially anti-HMGCR-positive disease, have produced mixed results. While some cohorts have shown elevated cancer rates,[18] others have reported malignancy rates

	Low Risk Features	Intermediate Risk Features	High Risk Features
Diagnosis	• ASyS • CTD-associated IIM • IBM* • Juvenile-onset IIM*	• CADM • PM • IMNM	• DM
Antibody Specificity	• Anti-SRP antibodies • ASyS-associated antibodies • Myositis associated antibodies	• Anti-SAE1 antibodies • Anti-HMGCR antibodies • Anti-Mi-2 antibodies • Anti-MDA5 antibodies	• Anti-TIF1-ɣ • Anti-NXP2
Clinicodemographic Factors	• Raynaud's phenomenon • Inflammatory Arthritis • ILD	• Male sex	• Age >40-45 years** • Persistent disease activity despite treatment • Dysphagia • Cutaneous necrosis

Figure 2. Idiopathic inflammatory myopathy-associated cancer risk factors; *courtesy of Eugene Krustev, MD*

Abbreviations: anti-HMGCR: anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; **anti-MDA5:** anti-melanoma differentiation-associated protein 5; **anti-NXP2:** anti-nuclear matrix protein 2; **anti-SAE:** anti-small ubiquitin-like modifier 1-activating enzyme subunit 1; **anti-SRP:** anti-signal recognition particle; **anti-TIF1-ɣ:** anti-transcriptional intermediary factor 1-gamma; **ASyS:** antisynthetase syndrome; **CADM:** clinically amyopathic dermatomyositis; **CK:** creatine kinase; **CTD:** connective tissue disease; **DM:** dermatomyositis; **IBM:** inclusion body myositis; **ILD:** interstitial lung disease; **IMNM:** immune-mediated necrotizing myopathy; **LDH:** lactate dehydrogenase; **PM:** polymyositis.

Cancer risk stratification in IMM can be guided by a combination of clinical subtype, the antibodies that are present, and clinicodemographic factors. All other risk factors are included in the IMACS cancer risk stratification guidelines.

* Both IBM and juvenile-onset-DM were excluded from the IMACS cancer screening guidelines but are usually not associated with malignancy.

** The IMACS guidelines consider age > 40 years as a high-risk factor; however, previous studies have suggested > 45 years.

*** There is a potential inverse relationship with muscle enzyme levels and cancer risk, meaning that patients with higher muscle enzyme elevations have a lower risk of cancer; however, this was not included in the cancer screening guidelines and requires further research to characterize this association.

comparable to those in the general population.[19] When cancers are detected in IMNM patients, they tend to occur in seronegative patients, those positive for anti-HMGCR antibodies, and in patients over 50 years of age.[16] One complicating factor is that anti-HMGCR-positive patients tend to be older, male, and have other co-morbidities,[20,21] all of which may contribute to increased cancer risk in this group. Given the mixed evidence on cancer risk in IMNM, recently-published guidelines on IIM cancer screening classify IMNM as having an intermediate cancer risk. Within this classification, anti-HMGCR-positive disease is considered to carry a greater risk, whereas anti-SRP-positive disease is associated with a lower risk.[2]

Overlap Syndromes

Several autoantibodies are commonly detected in patients with OM, including anti-ribonucleoprotein (anti-RNP), anti-polymyositis/scleroderma (anti-PM/Scl), and anti-Ku.[22] Clinically, OM is characterized by presentations that frequently overlap several connective tissue diseases, including IIM, systemic lupus erythematosus, and systemic sclerosis. Estimating cancer risk in OM has been difficult due to the heterogeneity of the manifestations and the lack of standardized classification criteria that can be used to study these patients. While rare cancers have been described in patients with anti-Ku positive OM, there is generally no strong or consistent association with malignancy.[23-25 REF] In patients with anti-PM/Scl positive OM, one study showed that cancer risk was comparable to that of the general population[26 REF]; however, another study reported cases of cancer in patients with anti-PM/Scl OM.[27 REF] Additionally, anti-RNP positivity is associated with mixed connective tissue disease (MCTD), which is considered a subset of OM. The

literature on cancer-risk in MCTD is primarily focused on patients with predominant features of systemic sclerosis. However, a few studies have focused on cancer in MCTD patients with IIM. Overall, there does not appear to be a strong association between cancer and MCTD.[28 REF] Several other autoantibodies have been associated with cancer in other connective tissue diseases, including anti-RNA polymerase III,[29 REF] anti-RNPC3,[30 REF] and anti-CENP-F,[31 REF] but future studies are needed to clarify their expression and cancer risk associations in IIM. In summary, evidence suggests that patients with OM tend to have a lower malignancy risk compared to the other IIM subtypes.[4]

Inclusion Body Myositis

Although IBM is classified as an inflammatory myopathy due to the frequent presence of inflammatory infiltrates on muscle biopsy, it typically is non-responsive to immunomodulating therapies. Furthermore, IBM tends to affect the distal upper limbs and proximal lower limbs, which makes it unique when compared to the other IIM subtypes.[32] Similar to anti-HMGCR-positive IMNM, IBM tends to occur later in life and is more prevalent in male patients,[33] which confounds cancer risk assessment in this population. Although cancers can be detected in IBM patients, their incidence is not different from age-adjusted controls. This suggests that older age, rather than the IBM diagnosis itself, is more likely contributing to cancer occurrence in these patients.[34] As such, IBM is generally not associated with co-incident malignancies; however, newer evidence would suggest that there may be an association with T cell large granular lymphocytic leukemia, which is an area of ongoing research.[35]

Polymyositis

The term PM is slowly falling out of favour as newer subtypes such as IBM, ASyS, and IMNM have been described. Many patients previously described as PM are now understood to fit better within these classifications.[36] The data on cancer risk in PM is confounded by the fact that historically the populations used to study cancer risk in PM likely contained patients from these other IIM subtypes. A metanalysis comparing PM to other IIM subtypes reported a significantly decreased risk of malignancy in PM, with an RR of 0.49 (95% CI 0.37, 0.65).[2] However, previous research has suggested an increased risk of malignancy in PM patients compared to the general population.[37] Given the mixed evidence regarding cancer risk in PM, the newly published guidelines classify PM as having an intermediate risk for malignancy.[4] As we continue to improve our classification criteria for IIM, future studies will be needed to determine the actual cancer risk amongst patients who truly meet the criteria for the PM subtype.

Juvenile-onset Idiopathic Inflammatory Myopathy

Juvenile-onset IIM (previously referred to as juvenile dermatomyositis) is defined as IIM diagnosed in a patient <18 years of age. Numerous studies have looked at cancer risk in juvenile-onset IIM, with most concluding that paraneoplastic juvenile-onset IIM is rare.[38-40] A review of the literature did find several case reports of cancer-associated juvenile-onset IIM; however, the rarity of these cases suggests that additional cancer-focused investigations should only be pursued in patients with additional signs or symptoms suggestive of an underlying cancer.[41]

Clinicodemographic Factors That Affect Cancer Risk in IIM

Similar to the general population, advancing age confers a higher malignancy risk in IIM (weighted mean difference 11.19; 95% CI 9.29, 13.08).[2] A meta-analysis has reported that the mean age at IIM-onset among patients with cancer-associated myositis is 59 years, compared to 49 years in those without cancer.[2] Practically speaking, patients over the age of 45 tend to be at the highest risk for developing cancer.[42] Additionally, multiple studies have identified male sex as another factor associated with an increased risk of malignancy in IIM (weighted mean difference 1.53; 95% CI 1.34, 1.75).[2,43]

Several disease manifestations have been associated with an increased risk of malignancy in IIM, including dysphagia (relative risk 2.09; 95%CI 1.21, 3.60), cutaneous ulcerations (relative risk 2.73; 95%CI 1.33, 5.59), and severe treatment-resistant disease.[2,42] In contrast, both Raynaud's phenomenon (relative risk 0.61; 95%CI 0.39, 0.95) and ILD (relative risk 0.49; 95%CI 0.32, 0.76) have been associated with a decreased risk of malignancy, likely because these manifestations are frequently present in ASyS patients.[2] Interestingly, patients with more pronounced elevations in muscle enzymes (creatine kinase and lactate dehydrogenase) had a decreased risk of

malignancy compared to those with more subtle elevations or normal muscle enzymes.[2]

Cancer Screening Guidelines

The newly released cancer screening guidelines from the International Myositis Assessment and Clinical Studies Group (IMACS) represent a monumental achievement for guiding cancer screening in newly diagnosed IIM patients. The following section summarizes a risk-based approach to cancer screening in IIM, with reference to the guidelines; however, the complete guidelines can be accessed in the original publication.[4] It is important to note that these guidelines do not apply to patients with juvenile-onset IIM or IBM, as cancer risk in these groups is comparable to age-matched controls from the general population. Furthermore, the guidelines only apply to IIM patients who are either within three years of diagnosis or up to three years after diagnosis, as cancer incidence tends to decline to levels closer to the general population beyond this timeframe.

Numerous regional cancer screening protocols apply to the general population and are influenced by factors such as country of residence, demographic factors, and family history. Cancer screening protocols that apply to the general population are based on multiple factors and are constantly evolving. Regardless of an individual's IIM cancer risk, all patients should continue to undergo routine cancer screening as recommended for their geographic location, age, sex, and family history.[4]

In addition to following routine cancer screening protocols, all patients should undergo a 'basic screening panel'. This includes a comprehensive history and physical examination to assess for possible signs of malignancy, complete blood count, liver function tests, erythrocyte sedimentation rate, c-reactive protein, serum protein electrophoresis, urinalysis, and a plain chest x-ray.[4]

Patients with IIM can be stratified into cancer risk categories based on their clinical and serological features. These cancer risk categories are not defined by precise numerical risk estimates, but are instead based on expert opinion and literature review for classifying manifestations based on how commonly they occur in IIM patients with co-incident malignancies. The following high-risk features each individually carry an increased risk of malignancy and include a diagnosis of DM, positivity for anti-TIF1-γ antibodies, positivity for anti-NXP2 antibodies, disease onset after age 40 years, persistently high disease activity despite immunosuppressive therapy, moderate to severe dysphagia, and the presence of cutaneous necrosis. Intermediate-risk factors comprise CADM, PM, IMNM, male sex, as well as positivity for anti-SAE1, anti-HMGCR, anti-Mi-2, and anti-MDA5 antibodies. Low-risk features include ASyS, positivity for ASyS antibodies, CTD-associated IIM, Raynaud's phenomenon, inflammatory arthritis, and ILD. Although the association of individual features with cancer risk has been studied, it is difficult to assign a precise level of risk based on the presence of any single characteristic. Furthermore, determining how to assign cancer risk in patients with multiple features, often including a mix of high and low-risk features, is an area of future study. Nonetheless, according to IMACS guidelines, cancer screening can be guided by attributing risk based on the number of high or intermediate risk features present in a given patient.

As per the IMACS guidelines, patients with either one 'high risk' feature or two 'intermediate risk' features are classified as having a moderate cancer risk. These individuals should undergo an enhanced screening panel that includes a CT scan of the neck, thorax, abdomen, and pelvis; cervical cancer screening; mammography; prostate-specific antigen blood testing; CA-125 blood testing; pelvic or transvaginal ultrasonography for ovarian cancer; and fecal occult blood testing.[4] It should be noted that some of these tests may already be part of routine, general-population-directed cancer screening. Clinicians should consider the timing of previously completed tests to avoid unnecessary duplication.

Patients exhibiting two or more high-risk features are considered candidates for intensive cancer screening strategies and should undergo both basic and enhanced screening at diagnosis, as well as yearly follow-up cancer screening with the basic panel.[2]

According to the IMACS guidelines positron emission tomography–computed tomography (PET-CT) should be considered in patients with a 'high risk' profile when both basic and enhanced screening panels fail to uncover an underlying malignancy.[4] They also suggest that clinicians consider PET-CT as a single screening procedure in patients with anti-TIF1-γ-positive DM with disease onset at >40 years of age and with ≥1 additional 'high risk' clinical feature, as these patients are at the highest cancer risk.[4] In these

very high-risk patients, PET-CT may eliminate the need for further tests while providing comparable diagnostic utility.[4]

The guidelines also recognize that certain regions have a high prevalence of nasopharyngeal carcinoma, and that in these regions nasopharyngeal endoscopy may be warranted.[4] Similarly, upper and lower gastrointestinal endoscopy may be justified in regions where gastrointestinal cancers are common. Additionally, for patients with high-risk symptoms, such as constitutional symptoms, a history of smoking, or a family history of malignancy, the authors recommend cancer screening regardless of their IIM-related risk profile.[4]

Since the publication of the IMACS cancer screening guidelines, several studies have looked at their performance in real-world settings. One retrospective study applied the guidelines to a cohort of 370 DM patients, of whom 18 patients (4.8%) were diagnosed with cancer. The authors found that the screening guidelines would have identified cancer in all of their cancer cases.[44] However, 338 patients (91.3%) would have been classified as high or moderate risk as per the guidelines, and therefore would have undergone extensive screening. The authors concluded that strict adherence to the guidelines may result in unnecessary testing for some patients. Another study conducted in an Australian cohort observed that many patients would have been considered 'under-screened' prior to the publication of the guidelines. Implementation of the guidelines would significantly increase the number of screening tests ordered. The authors also concluded that applying the screening guidelines could potentially increase costs compared to previous practices and may not be available in under-resourced areas.[45] An evaluation of the IMACS guidelines in a Hong Kong cohort demonstrated that the criteria performed well for identifying malignancies in the high-risk group; however, few cancers were detected in the intermediate-risk group.[45] Overall, the results of these studies show that while the IMACS criteria offer high sensitivity for cancer detection, they may also lead to over testing due to the breadth of these recommendations. Future prospective studies are needed to assess if the new screening guidelines improve the stage of cancer diagnosis and patient survival.

One possible solution to help avoid over-screening while applying the IMACS guidelines in clinical practice is a step stepwise approach. Both the basic screening and enhanced screening protocols are amenable to stepwise implementation where basic screening would be performed first, followed by further imaging that might be directed by relevant findings on basic screening. If a malignancy is identified early in the process, then further testing could be halted or redirected toward a more targeted approach, thus reducing the number of lower-yield tests. The exact order of testing will need to be decided based on individual patient risk factors, and future research is needed to assess if this is a feasible approach. Additionally, one downfall of taking a step wise approach is the potential risk of diagnostic delay. Therefore, clinicians should only consider this strategy when scheduled short term follow-up is feasible.

Emerging Diagnostics and Future Directions

The use of myositis-specific autoantibodies, especially anti-TIF-1-ɣ, are an essential part of risk stratification in IIM. Interestingly, the novel autoantibodies anti-CCAR1[46] and anti-SP4[47] have been shown to decrease cancer risk in DM patients. One proposed explanation is that patients with multiple antibody positivity may mount a more effective anti-tumour immune response, leading to the successful elimination of malignant cells.[48] Currently, testing for these antibodies is not widely available in clinical practice. Further research is needed for us to better understand how these antibodies might be integrated into risk stratification models, such as those outlined in the IMACS guidelines.

Conclusions

IIM represents a heterogenous group of diseases, each with distinct cancer risk profiles. Within each IIM subtype, cancer risk also varies depending on specific antibodies and clinicodemographic factors. The recently-published IMACS guidelines provide an effective framework for cancer screening in IIM; however, future research is needed to clarify these strategies for greater efficiency and precision in cancer screening. Future studies should focus on optimizing cancer screening approaches in IIM, as well as evaluating the clinical utility of novel biomarkers to provide a precise cancer risk assessment.

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What Can We Tell Our Patients About Rheumatoid Arthritis Risk?

Liam O'Neil, MD, MHSc, FRCPC
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Introduction

You are seeing a 45-year-old female with a chief complaint of joint pain in the hands and feet. The symptoms have been apparent for 6 months. There was no preceding illness. She reports morning stiffness of the affected joints. The patient denies any joint swelling. Her medical history is notable for a strong family history of Rheumatoid Arthritis, and she currently smokes one pack of cigarettes daily. On physical examination, the joints appear normal, with full range of motion and no obvious tenderness to palpation. There is no evidence of synovitis or rashes. Laboratory investigations show elevated anti-citrullinated protein antibody level of 135, and her rheumatoid factor level is 45. C-reactive protein is within normal limits. Radiographs of the hands and feet are normal.

Questions:
1. What is her likelihood of developing rheumatoid arthritis within the next 3 years?
2. Are there any other tests you need to order?
3. Can rheumatoid arthritis be prevented in this individual? What advice can you provide her?

Rheumatoid Arthritis (RA) is an autoimmune inflammatory arthritis of unknown etiology. RA patients typically present with joint swelling in the hands and feet along with serological markers such as anti-citrullinated protein antibodies

(ACPA) and Rheumatoid Factor (RF).[1] RA is thought to begin with a set of risk factors, including genetics, sex, and environmental influences. Although numerous genetic loci have been linked to RA development, RA is strongly associated with the presence of a specific HLA-DRB1 risk allele termed the shared epitope.[2] Females are more predisposed to develop RA compared to males (often with a ratio of 4:1), and while this association is poorly understood, sex hormones and pregnancy likely play an important role. The external environment is also associated with RA development. Dietary factors, for example diets that are low in omega-3 fatty acids; (these are derived primarily from fish), along with environmental exposures such as air pollution and cigarette smoke are all linked to RA.[3] Having a first-degree relative with RA increases an individual's risk of developing the disease, likely due to a contribution of shared genetic factors and potentially similar environmental exposures. Approximately 70% of RA cases are seropositive (ACPA/RF positive), and in those that do develop autoantibodies, these appear years before the onset of clinically detectable arthritis. As such, ACPA has served as one of the best prediction markers for RA development. Although RA may start abruptly, many individuals experience non-specific joint symptoms suggestive of RA such as pain and stiffness in the hands and feet prior to the development of evident inflammatory arthritis.

What Is Her Likelihood Of Developing RA Within The Next 3 Years?

Research cohorts comprised of individuals at risk for developing RA have provided key insights into the pathogenesis of the preclinical disease stages of RA. Depending on the inclusion criteria for enrolment, a varying proportion of participants in these studies will develop RA after extended follow-up. Comparing those who develop RA with those who do not provides the opportunity to identify factors that are predictive of these outcomes. The individual in question has several important risk factors to suggest the risk of developing RA is quite high. Her family history of RA perhaps suggests that her polygenic risk score may be high, and although genotyping data are typically not clinically available, perhaps she carries the shared epitope HLA-DRB1 risk allele. Assuming she does, this allele has been shown in prior studies (mostly case-control) to interact synergistically with cigarette smoking (another risk factor in her case) by increasing the risk of RA by up to 15-fold.[5] She also meets all the criteria for clinically suspect arthralgia (CSA), in which approximately 20% of individuals develop arthritis within 2 years, though estimates vary.[6] The detection of ACPA has been demonstrated to be a highly reliable biomarker for predicting future RA. Moreover, the concentration of ACPA is an independent predictor for developing RA, with higher antibody levels corresponding to a greater risk of disease development.[7] Additionally, the presence of both ACPA and RF further increases the risk of developing RA.[8] While the exact risk associated with ACPA positivity varies depending on the cohort and testing methods used, approximately 35% of ACPA-positive individuals develop RA within 5 years.[7] Importantly, in individuals with both ACPA positivity and small joint arthralgia, the risk of progressing to clinical RA may be as high as 40% within 2 years. You counsel her that her risk of developing RA within the next 3 years likely exceeds 40%.

Are There Any Other Tests You Need To Order?

Several studies have examined the role of imaging modalities in predicting the risk of RA, specifically the use of ultrasound (US) and magnetic resonance imaging (MRI), with a focus on detecting subclinical synovitis. In US, the most specific findings suggestive of future RA include power Doppler signal, grey scale abnormalities and erosions. For MRI, features such as bone marrow edema, tenosynovitis/synovitis, and erosions are considered highly specific. In general, imaging findings in preclinical RA lack sensitivity, and as such, their absence does not rule out future RA in individuals with other risk factors. Among those with arthralgia, the combination of ACPA positivity and MRI-detected inflammation is associated with progression rates as high as 70%.[6] However, in the same study, the rate of progression among ACPA-negative individuals with MRI-detected inflammation was much lower, at 18%. Similarly, US findings in ACPA-positive individuals with arthralgia, the presence of bone erosion and synovitis was associated with a progression rate of 68% within 2 years. In contrast, when US findings were absent, the rate dropped to 15%.[9] To support risk stratification, comprehensive scoring systems have been developed in arthralgia cohorts, through weighted variables to generate a risk score allow for risk stratification of RA. Clinical features such as arthralgia, morning stiffness,

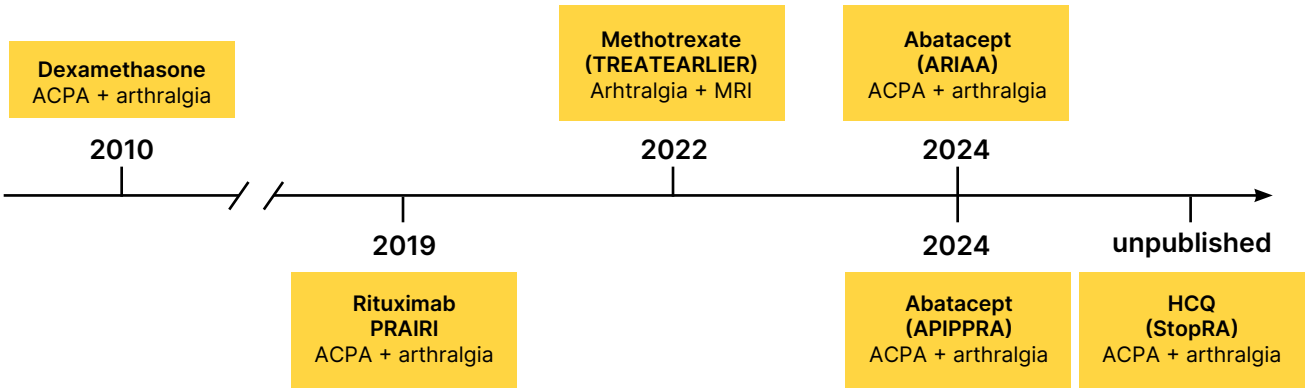

Figure 1. A summary of completed Rheumatoid Arthritis Prevention clinical trials and their major inclusion criteria; *courtesy of Liam O'Neil, MD, MHSc, FRCPC and Hani El-Gabalawy, MD, MHSc, FRCPC*

Abbreviations: ACPA: anti-citrullinated protein antibodies; **MRI:** magnetic resonance imaging

ACPA, and RF can collectively achieve thresholds of risk that exceed 50%.[10] While imaging likely provides added value, the cost-benefit of these approaches, particularly in very high-risk clinical profiles, remains somewhat unclear.

Magnetic resonance imaging or ultrasound can help detect subclinical synovitis and may aid in predicting future RA.

However, routine use of these imaging tests may not be feasible in many centres, and their added value in individuals with very high-risk profiles needs to be clarified. It is also uncertain what to do with positive results on imaging without clinical synovitis.

Can RA Be Prevented In This Individual? What Advice Can You Provide Her?

The first clinical trial aimed at RA prevention was published in 2010 and evaluated the effects of dexamethasone or placebo in 83 individuals with arthralgia and RA-related autoantibodies.[11] This trial showed no difference in the development of clinical arthritis after 2 years. This initial trial was followed by several others investigating repurposed RA medications including rituximab,[12] methotrexate,[13] abatacept[8,14] and hydroxychloroquine **(Figure 1)**. Largely, these trials shared a similar design, which was to provide participants with the active drug for a defined period (6 to 12 months), followed by a withdrawal period where individuals received no therapy. Rituximab, methotrexate, and abatacept showed efficacy in delaying the onset of RA during the active treatment phase. However, this protective effect tended to decrease during the treatment-free period. In 2 RCTs using abatacept, the preventative effects of the intervention remained statistically significant through the study follow-up period, showing sustained prevention of inflammatory arthritis.[13,14] However, long term follow up data shows that prevention disappears after about 3 years.[15] This finding differs from methotrexate and rituximab trials, which did not show persistent prevention of ACPA+ RA at the end of follow-up. In a subgroup analysis, methotrexate was shown to prevent ACPA- RA in individuals with joint pain and MRI inflammation.[16] Hydroxychloroquine and atorvastatin have not been shown to prevent RA among ACPA-positive individuals with arthralgia. Notably, the VITAL study, which was a placebo-controlled study evaluating 5 years of vitamin D and Omega-3 fatty acid supplementation, showed a preventative effect on the incidence of autoimmune disease, including a reduction in RA risk.[17] The total number of RA cases were low, and this was a pre-specified exploratory endpoint, rather than a primary outcome of the study. Further, since the study population was not screened for ACPA at baseline, it remains unclear how applicable these findings are to individuals with high-risk profiles.

Currently, there are no specific guidelines for managing individuals at risk of developing RA. Therefore, any advice provided should be pragmatic, focusing on lifestyle modifications that may reduce risk, while clearly acknowledging the limited evidence supporting these strategies.[18] A notable example is advocating for smoking cessation. Smoking is a well-established risk factor for RA and is associated with poor disease outcomes once RA develops. Moreover, all

individuals who smoke should be encouraged to quit due to the broader health risks associated with smoking, including cancer, cardiovascular disease, and chronic obstructive pulmonary disease. Diet is another modifiable factor; some evidence suggests that diets rich in omega-3 fatty acids, such as the Mediterranean diet or omega-3 fatty acid supplementation, may help reduce RA risk,[3] a finding supported by the VITAL study. Similar to smoking cessation, dietary changes may also offer broader health benefits. Finally, given the relatively high likelihood of progression to RA, annual follow-up is a reasonable approach. Educating individuals about the early signs and symptoms of RA will aid in timely diagnosis and treatment, which is known to significantly improve long-term outcomes.

Currently, there are no treatment guidelines for preventing RA, and further studies are needed before interventions can be recommended. Practical advice that can be provided to this patient includes: 1) Annual follow-up and education 2) Strongly advise her to quit smoking and provide her with resources to help her quit, and 3) Dietary changes.

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