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The pivotal role of Interleukin-23 in the skin-gut-joint axis

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ABSTRACT

Interleukin-23 (IL-23) plays a pivotal role in the intricate interplay between the skin, gut, and joints, contributing significantly to the pathogenesis of various inflammatory diseases including psoriasis, psoriatic arthritis (PsA), inflammatory bowel disease (IBD) and Behcet's disease. In recent years, several IL-23 inhibitors have been granted approval for the treatment of psoriasis, PsA and IBD. As up to one-third of patients diagnosed with psoriasis may go on to develop PsA and given the strong immunogenetic pathway incrimination of the IL-23 pathway in both psoriasis and PsA, dermatological lead therapy for psoriasis may therefore delay the development of PsA. Furthermore, patients with psoriasis or PsA are associated with increased risk of developing IBD. There is also evidence for psoriasis-directed therapy preventing IBD in keeping with the known pivotal role of IL-23 in both intestinal homeostasis and in the pathogenesis of IBD, including ulcerative colitis and Crohn's disease. This review discusses the multifaceted roles of IL-23 in regulating immune response and maintaining tissue homeostasis within the skin-gut-joint axis. In particular, the use of IL-23 inhibitors in trials in patients with psoriasis, IBD and PsA patients will also be discussed in relation to reverse translational immunology insights around inflammation in these domains.

1. Introduction

Historically, all inflammation against self was viewed under the autoimmunity rubric that most broadly equated with humoral autoimmune responses and autoantibodies [1]. A group of clinically overlapping diseases including psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis (AS), and Behcet's disease have been collectively placed under the seronegative spondyloarthropathy spectrum disorders while other immune-mediated inflammatory conditions such as Crohn's disease (CD) and ulcerative colitis (UC), frequently accompany spondyloarthritis (SpA) [2,3]. Historically, these conditions have been designated as autoimmune but these diseases lack autoantibodies and also the female preponderance typically noted in autoimmune diseases [4]. During the genome wide association study (GWAS) revolution that occurred just under two decades ago, investigators working independently on the aforementioned diseases independently established SNPs in the interleukin-23 receptor (IL-23R) and interleukin-23 (IL-23) cytokine genes and related Janus kinase (JAK) signalling as a common denominator [5,6].

A wealth of immune data and translational therapeutics has since validated IL-23 as a major differentiator between the classically recognised autoimmune diseases versus overlapping inflammatory diseases of gut, skin and skeleton. IL-23 is primarily produced by myeloid cells, articularly activated dendritic cells, macrophages, and monocytes at mucosal and entheseal sites in response to microbial or stress stimuli [7–9]. In contrast to classical autoimmunity, B cells play a limited role in these IL-23-driven processes, reflecting the autoinflammatory rather than autoantibody-mediated nature of SpA and related conditions

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[9–12]. Indeed, IL-23 stands at the crossroads of a complex interplay between the skin, gut, and joints, coordinating immune responses that underline the pathogenesis of various immune-mediated inflammatory diseases (IMIDs) [7,8,13–20]. The aim of this review is to describe the role of IL-23 in mastering inflammation within the skin-gut-joint axis, initiating the development of IMIDs in this context. Currently approved treatments directed at IL-23 in these settings will also be reviewed.

2. Basic IL-23 biology

IL-23 is a heterodimeric cytokine composed of p19 and p40 subunits and plays a central role in driving inflammation and tissue damage in a range of immune-mediated conditions [9,10,21]. The p40 subunit is shared with IL-12 while the p19 subunit is exclusive to IL-23 in humans although the p19 subunit may form an alternative heterodimeric cytokine in murine models [22].

Upon binding to its receptor, IL-23 activates downstream signalling pathways via JAK2 and TyK2 signalling leading to the phosphorylation and activation of transcription factors such as signal transducer and activator of transcription (STAT)3 and retinoic acid receptor-related orphan receptor gamma t (RORγt) [7,8,13,23–27], leading to the production of pro-inflammatory cytokines, notably interleukin-17A (IL-17A), IL-17F and interleukin-22 (IL-22) [28–30], but also other pro-inflammatory cytokines including TNF and granulocyte-macrophage colony-stimulating factor (GM-CSF).

The biological activity of IL-23 is mediated through interaction with its receptor complex, which consists of two subunits: IL-23R and IL-12Rβ1. IL-23R is the specific receptor subunit for IL-23, while IL-12Rβ1 is shared with the IL-12 receptor [31,32].

IL-23 and IL-12 are similar in structure and in their ability to stimulate interferon-gamma (IFN-γ) memory T cell proliferation, however, only IL-23 preferentially induces proliferation of Th17 cells which produce IL-17. In this regard, IL-23 can be considered a master cytokine in the development and maintenance of the novel "autoimmunity" associated with psoriasis, PsA and inflammatory bowel disease (IBD). Although IL-12 is a potent cytokine that drives T-cell responses including IFN-γ and tumour necrosis factor (TNF) production, it is also a regulatory cytokine with anti-inflammatory roles [33] in addition to a role in host protective immunity. Therefore, treatments that target only the IL-23 p19 subunit and not the p40 subunit, preserve IL-12 function and potentially reduce side effects while providing more targeted treatment for IL-23 driven diseases.

This supports the rationale for selective IL-23 (p19) inhibition as a more targeted therapeutic approach rather than dual IL-12/23 (p40) blockade [7,23,34,35]. IL-12 plays a role in protective Th1 responses and immune surveillance, and its concomitant inhibition may blunt beneficial host defence [9,30,31]. In contrast, p19-specific inhibition spares IL-12 while effectively suppressing IL-23–driven Th17-mediated inflammation, resulting in superior clinical outcomes across psoriasis, PsA, and IBD [7,9,28,36,37].

However, IL-17 production is not entirely dependent on IL-23 signalling. Other cytokines such as IL-1β, IL-6, IL-21, and IL-7 can induce or sustain IL-17 expression through innate-like lymphocytes including γδ T cells, MAIT cells, ILC3s, and tissue-resident memory T cells [38–41]. This IL-23-independent IL-17 production may contribute to persistent axial inflammation in PsA, highlighting the complexity of cytokine networks in these manifestations.

Recent clinical data further support the role of IL-23 inhibition in PsA, including axial phenotypes. In a multicentre prospective study, guselkumab significantly improved BASDAI, ASDAS, and MRI sacroiliac joint scores after four months of treatment in patients with PsA and axial involvement [42]. These findings reinforce the therapeutic relevance of IL-23 blockade in psoriatic disease, while acknowledging IL-17-driven inflammation may persist via IL-23-independent mechanisms.

3. IL-23 and the skin

In the context of the skin, IL-23 has emerged as a central player in the pathogenesis of psoriasis [43]. IL-23 promotes the differentiation and activation of T helper 17 (Th17) cells, which produce IL-17 and IL-22, implicated in the development and maintenance of psoriatic lesions [13,44–47]. IL-23 and its receptor IL-23 receptor are also expressed in keratinocytes of skin lesions [48–50]. Furthermore, IL-23-driven inflammation in the skin [51] is associated with keratinocyte hyperproliferation, aberrant immune cell infiltration, and disrupted epidermal barrier function, contributing to the characteristic clinical manifestations of psoriasis [52–55]. Myeloid cells are the main producers of cutaneous IL-23 and T-cells, the main expressors of the IL-23R. However, there is evidence of a more complex cutaneous biology with the barrier tissues themselves directly involved in the IL-23 biology.

IL-23 is recognised to target $CD4^+$ as well as $CD8^+$ tissue resident memory (TRM) T-cells influencing the differentiation and proliferation of Th17 cells [13,56,57]. TRM cells have been shown to contribute to autoimmune diseases like psoriasis, causing chronic inflammation and recurring lesions [58]. Furthermore, targeting IL-23p19 has been shown to suppress TRM cells, promoting a beneficial shift in the balance between $CD8^+$ TRM cells and regulatory T cells, leading to longer-lasting therapeutic effects in psoriasis compared to IL-17A inhibition [7,57].

In addition to its effects on T cells, IL-23 also modulates the function of other immune cells, including dendritic cells, macrophages, and innate lymphoid cells [7,13,59]. In psoriasis, the proliferation of Th17 cells and increased secretion of IL-17, which are initiated by IL-23, create a positive feedback loop that augments the inflammatory response leading to increased keratinocyte proliferation [45,60,61]. Besides dermal dendritic cells, epidermal keratinocytes and dermal macrophages have also been identified as sources of IL-23, potentially playing a role in the development and persistence of psoriatic plaques [49,62].

Preclinical studies have advanced our understanding of the role of IL-23 in psoriasis. Injection of IL-23 can trigger erythema and induration in mice that resemble psoriatic lesions [61,63]. Moreover, increased IL-17C levels, especially when combined with other pro-inflammatory molecules, result in psoriatic skin-like symptoms in mice [64,65]. The skin serves as both a barrier and a sensory interface, housing immune cells like dermal dendritic cells (DDCs) and IL-17-producing γδ T cells, which contribute to psoriasis when activated by IL-23. Riol-Blanco and colleagues demonstrated that sensory neurons expressing the ion channels TRPV1 and NaV1.8 are essential for IL-23 production by DDCs in imiquimod-induced inflammation [66]. Denervation blocks this psoriasis-like response by disrupting nociceptor-DC communication, reducing IL-23-driven cytokine production and inflammatory cell recruitment. Intradermal IL-23 injection restores inflammation, highlighting the neuroimmune regulation of IL-23 and its role in cutaneous immune responses.

In humans, elevated IL-23 and IL-17 in human psoriatic plaques and serum has intensified research into the IL-23/Th17 axis and its role in the development psoriasis [64,65]. Supporting pre-clinical data, elevated levels of IL-23 have been observed in psoriatic plaques compared to non-lesional skin, suggesting its critical role in disease pathology [45,51].

Alefacept, a fusion protein that inhibits $CD4^+$ and $CD8^+$ T cell activation, resulted in histological remission in 55 % of psoriatic patients, with reductions in lesional lymphocytes (73 %), CD8 cells (79 %), and inflammatory gene expression, including IL-23. Responders also had decreased dendritic cells in psoriatic lesions [67]. In another study, anti-IL-12p40 treatment reduced IL-12/IL-23 levels, along with IFN-γ, chemokines (IL-8, Interferon Gamma-induced Protein-10; IP-10, monocyte chemoattractant protein-1; MCP-1), TNF-alpha, and T cells, with greater reductions seen in high responders, preceding clinical improvements [68].

4. IL-23 and the gut

Beyond the skin, IL-23 plays a critical role in the pathogenesis of IBD, predominantly CD and UC [14,69,70]. In the gut, dysregulation of IL-23 signalling contributes to chronic intestinal inflammation, mucosal damage, and barrier dysfunction [7,14,69]. Several studies have demonstrated elevated IL-23 levels and increased Th17 cell infiltration in the inflamed intestinal mucosa of IBD patients, highlighting the involvement of IL-23-mediated pathways in disease pathogenesis [69,71,72]. Several key innate immune cell populations including group 3 ILCs, gamma delta T-cells and mucosal-associated invariant (MAIT) T cells that act as barrier sentinels are also critically dependent on IL-23R signalling and subtly control intestinal homeostasis in health [23,73,74]. The regulatory role and role of IL-23 in tissue repair in intestinal homeostasis is recognised by the fact that the downstream T-cell derived cytokines namely IL-17A and IL-22 also play multifaceted roles in tight junction formation and in crypt cell proliferation and homeostasis [73,75].

The pathogenesis of IBD is complex and involves a dysregulated immune response to intestinal microbiota in genetically susceptible individuals [76,77].

In the healthy gut, IL-23 expression is tightly regulated [23,78,79]. However, dysregulation of IL-23 signalling contributes to chronic intestinal inflammation, mucosal damage, and barrier dysfunction [7,14,69]. Specific cell types, including FcγRI/CD64+ monocyte/macrophage in addition to FcγRI/CD64+ neutrophils have been identified as IL-23 producers in IBD patients [80,81].

Moreover, the overexpression of IL-23 contributes to impaired intestinal barrier function and exacerbates inflammation through downstream signalling pathways [7,14,69,70]. This activation promotes the differentiation, survival, and expansion of Th17 cells [70,82].

Several studies have demonstrated elevated levels of IL-23 and increased Th17 cell infiltration in the inflamed intestinal mucosa of IBD patients, highlighting the involvement of IL-23-mediated pathways in disease pathogenesis [69,71,72,83].

Regulatory T cells, essential for regulating and suppressing chronic inflammation, are found in reduced numbers in individuals with IBD [84] and IL-23 signalling has been implicated in inhibiting regulatory T cell differentiation, further exacerbating the inflammatory response [70,85,86].

This IL-23-mediated suppression of regulatory T cell differentiation contributes to an imbalance in the gut immune environment, favouring pro-inflammatory Th17 responses over regulatory pathways [87]. Evidence from studies have shown that this imbalance can worsen gut inflammation, highlighting the need for therapies targeting the IL-23/Th17 axis to restore immune homeostasis in IBD [69,87–89]. There is other evidence showing that IL-23, rather than IL-12, is crucial in CD-ileitis progression [90]. It was found in fact, that IL-23 deficiency reduced immune cell infiltration and cytokine expression in the ileum; moreover, IL-23 appears to function independently of IL-17.

It is also recognised that IL-17 plays a dual role in the intestine since it can drive inflammation, contributing to IBD, but is also recognised to exert protective effects [36,91]. Consequently, IL-17 inhibitors often fail or worsen IBD, highlighting the complex balance between IL-17's inflammatory and protective functions in gut health [36,92,93].

Although different myeloid cells including dendritic cells and macrophages produce IL-23, the main cell type responsible for IL-23 production in the intestine in IBD is the neutrophil [81]. This finding was replicated in the murine SKG model that also develops colitis and associated spondyloarthropathy spectrum inflammation where the skeletal neutrophils were the earliest source of entheseal inflammation and also entheseal IL-23 transcript expression [94].

In the intestine, analogous to the skin keratinocyte barrier, enterocytes can also locally produce IL-23 that provides for exquisite regulation of local intestinal T-cell responses [41,95]. Furthermore, in murine models, intestinal epithelial IL-23R expression is key to normal commensal microbiotal interaction and innate antimicrobial responses [41].

5. IL-23 and the joint

It is believed that IL-23 (and its receptor, IL-23R) plays a key role in the pathogenesis of PsA and SpA, as altered levels or expression of this interleukin are found in various anatomical locations affected by these disorders [7,96]. This in turn leads to an increase in various immune cells expressing IL-23R, such as Th17 cells, γδ T cells, ILC3s, and CD8+IL-23R + mucosal-associated invariant T cells, in the joints and entheses of SpA and PsA patients [7,10–12,97,98].

In humans, peri-entheseal $CD14^+$ monocytic lineage cells are the main source of inducible IL-23 [99]. Peri-entheseal neutrophils are also a major source of inducible IL-23 in humans [94]. Given that neutrophils are abundant in the spinal bone marrow but scare in the peripheral fatty marrow it has been proposed that this could be a major factor in the efficacy of IL-23 inhibitors in the peripheral skeleton but not for bone osteitis in AS [98].

IL-23 has since been implicated in driving joint inflammation [100–102], thereby highlighting its importance in rheumatological diseases.

IL-23 activates Th17 cells within the joint environment, leading to the secretion of IL-17, which recruits other inflammatory cells such as neutrophils and macrophages [96,102]. IL-23 acts through the IL-23–IL-17 axis, recruiting IL-17/IL-23-producing $CD4^+$ T helper cells, innate lymphoid cells, and γδ T cells to the joints, where they release IL-17, IL-21, IL-22, and GM-CSF [103,104]. This cytokine cascade amplifies local inflammation, leading to joint pain, synovitis, and cartilage degradation [105–108]. IL-23 also drives osteoclastogenesis by upregulating receptor activator of nuclear factor kappa-B ligand (RANKL) expression in synovial fibroblasts, promoting bone resorption and erosion [109–111].

Increased IL-23 expression has been detected in the synovial tissue and fluid of PsA patients compared to those with non-inflammatory conditions, indicating its key involvement in PsA pathogenesis [112,113]. Furthermore, in patients with higher synovitis scores, IL-23-related gene expression is elevated, correlating with more severe disease [114].

A recent study by Lee et al. used a zymosan-induced arthritis model in wild-type and IL-23p19−/− mice to identify IL-23p19-expressing cells and test the effects of IL-23p19 blockade [115]. Their findings showed that non-bone marrow-derived macrophages are essential for arthritis development, and blocking IL-23p19 reduced pain and disease symptoms.

IL-23 is also crucial in the development of enthesitis, a hallmark feature of SpA (including PsA) [12,116,117]. In the seminal work by Sherlock, it was demonstrated that IL-23 is essential in enthesitis, acting on specific subsets of entheseal resident T cells [11].

Cuthbert and colleagues explored the presence of IL-23/IL-17 axis cytokines in normal human spinal entheses and confirmed the ILC3 phenotype at entheses by showing RORγt, STAT3, and IL-23 receptor transcript expression [118]. Cytokine profiles of ILC3s from entheses were similar to those from SpA synovial fluid and IL-23/IL-1β stimulation increased IL-17A transcript, and histology of damaged entheses showed RORγt-expressing cells [118]. IL-23 stimulates these cells to produce IL-17, leading to localized inflammation, recruitment of inflammatory cells, and subsequent tissue damage at the enthesis [118]. The same group previously observed macrophages in acute enthesitis, suggesting possible local IL-23 production at the enthesis [119]. Further investigation revealed that IL-23 production can be induced in normal enthesis by $CD14^+$ myeloid cells following bacterial or fungal stimulation [99].

IL-23 inhibitors have demonstrated inefficacy in treating AS, however, they might have a positive effect on axial PsA (axPsA), highlighting critical differences in how these conditions respond to treatment [120].

Studies comparing the two conditions reveals distinctions in clinical presentation, such as the more prominent role of enthesitis in PsA and the association of HLA-B27 with AS. Imaging findings also differ, with AS showing more extensive bone involvement, while PsA exhibits characteristic ligamentous soft-tissue changes [121,122]. These anatomical and immunological variations likely contribute to the differing responses to IL-23 inhibitors. Ongoing studies are focusing on better defining axPsA to improve diagnosis and treatment. The need for clearer classification criteria for axPsA remains a key challenge, as it could enhance both diagnostic accuracy and the development of targeted therapeutic strategies.

It also remains to be understood why IL-23 inhibition blocks the onset of murine arthritis in the spine but fails as a therapy for established axial spondyloarthritis (axSpA) [123]. Although IL-23 is vital in initiating Th17-driven inflammation, clinical trials with IL-23 inhibitors, such as risankizumab [124] and ustekinumab [125], showed no significant benefit in AS. Genetic studies suggest IL-23R variants contribute to disease susceptibility, but its precise role in axSpA still remains unclear. IL-23 may influence disease onset but seems to become less important in chronic stages with other cytokines such as IL-12 and IL-18 having a predominant role [39]. Additionally, it is thought that innate immune cells produce IL-17 and can contribute to inflammation, independent of IL-23 stimulus [38–40].

Higher doses of IL-23 inhibitors may be needed in PsA compared to psoriasis, based on findings from the DISCOVER-2 trial with guselkumab [18,126]. The trial demonstrated that while guselkumab, an IL-23 inhibitor, was effective in treating psoriasis at a standard dose (100 mg every 8 weeks), PsA patients required higher doses (100 mg every 4 weeks) to achieve optimal therapeutic responses. In PsA, the inflammatory pathways and joint involvement may necessitate more robust inhibition of IL-23, as the disease pathogenesis involves a combination of synovitis, enthesitis, and osteitis, which are less prominent in psoriasis [127]. This finding is consistent with other studies showing that PsA may require stronger or more frequent dosing of biologics due to the complexity of the disease [127–129].

Taken together, these findings show that IL-23 is a central orchestrator of inflammation in SpA, linking intestinal, skin, and joint inflammation (Fig. 1). with a crucial role in the development of enthesitis. This highlights the therapeutic potential of targeting IL-23 in managing SpA and related diseases.

6. IL-23 as a therapeutic target in psoriasis

There are currently three approved IL-23 inhibitors (all three are p19 subunit antagonists) for the treatment of moderate-to-severe psoriasis: risankizumab, tildrakizumab and guselkumab [130–132].

Guidelines do not provide specific recommendations on which biologic drug should be selected as a first-line treatment based on factors such as disease severity, involvement of challenging-to-treat areas, or the presence of cardiometabolic comorbidities [133]. IL-23 inhibitors

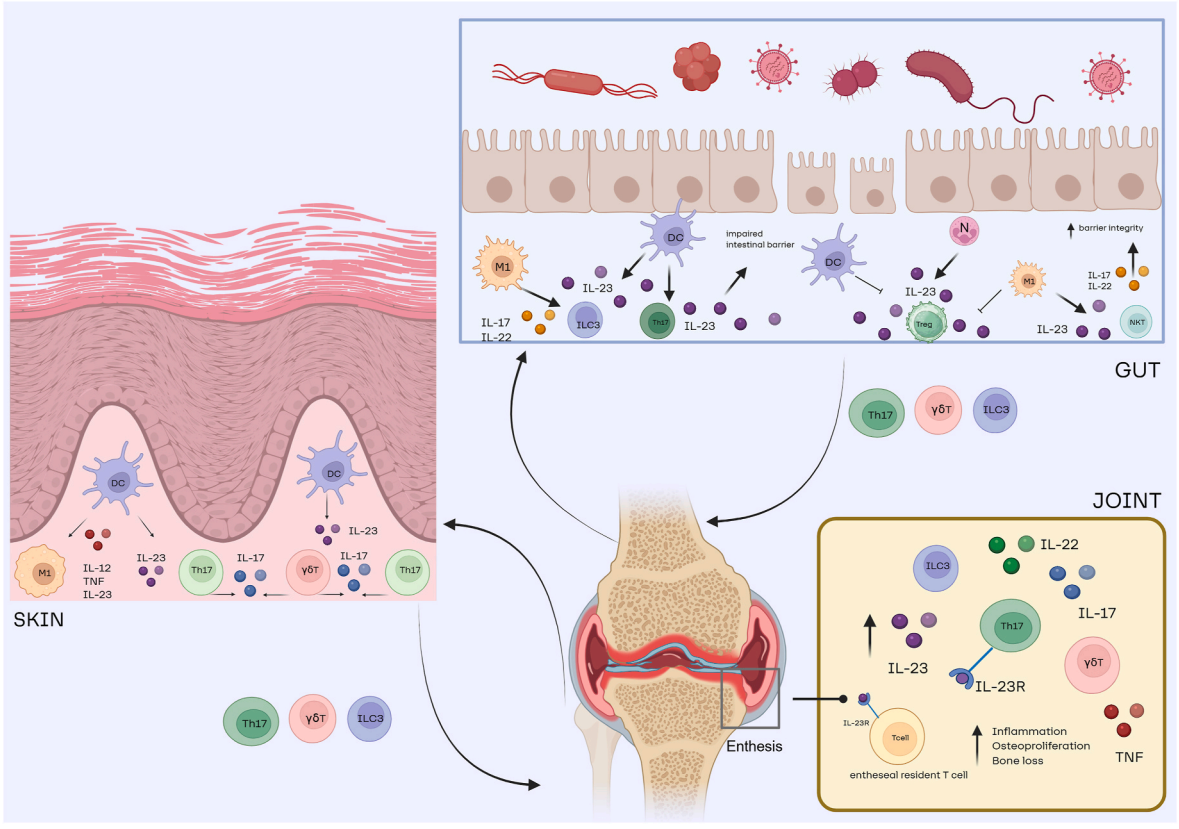

Fig. 1. Mechanistic overview of IL-23 in skin, gut, and joint inflammation via th17 and innate cells. in psoriasis IL-23, produced by dendritic cells, keratinocytes and dermal macrophages, promotes Th17 differentiation and modulates the function of other immune cells, including macrophages, and ILCs. In IBDs the overexpression of IL-23 contributes to impaired intestinal barrier function and exacerbates inflammation through downstream signalling pathways: differentiation and expansion of Th17 cells, inhibition of Treg cells, which favour pro-inflammatory IL-17 mediated responses and reduce the IL-17 protective responses on barrier integrity, activation of ILC3 and γδ T cells, both with pro-inflammatory activity. IL-23-activated Th17, ILC3 and γδ T cells, migrate from skin and gut to the joints. In the joint local expression of pro-inflammatory cytokines, including IL-23 drive inflammation and articular damage. IL-23 activates Th17 cells, innate lymphoid cells, entheseal resident T cells and γδ T cells, where they release IL-17, IL-21, IL-22, promoting chronic inflammation, osteoproliferation and bone loss. At the enthesis, IL-23 acts directly on entheseal-resident T cells expressing IL-23R, leading to their activation and production of IL-17, IL-22, and TNF. This promotes local inflammation, enthesitis, osteoproliferation, and bone remodeling. Together, IL-23–responsive Th17, γδ T, and ILC3 populations amplify joint and peri-entheseal inflammation, linking mucocutaneous and articular immune pathways. *Created in BioRender. (2025)*https://BioRender.com/c93h486

are typically recommended for adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy. A summary of the efficacy of approved IL-23 inhibitors in patients with moderate-to-severe psoriasis in terms of PASI 75 or PASI 90 response is shown in Table 1.

Risankizumab (approved April 2019) is given as 150 mg subcutaneously; SC, at weeks 0, 4, then every 12 weeks [132]; guselkumab (approved July 2017) is given as 100 mg SC at weeks 0 and 4, then every 8 weeks; tildrakizumab (approved March 2018) is administered at 100 mg SC at weeks 0 and 4, then every 12 weeks. They have all demonstrated significant efficacy in phase III clinical trials. Risankizumab and guselkumab both outperformed adalimumab with 72 % and 47 % of patients achieving PASI90 at week 16 with risankizumab and adalimumab respectively [134] and 85.1 % of guselkumab-treated patients achieving clear or minimal psoriatic lesions by week 16, compared to 65.9 % with adalimumab [15], as emerged from the IMMvent and VOYAGE 1 trials. Risankizumab and guselkumab were also superior to secukinumab in patients with moderate-to-severe plaque psoriasis after 52 and 48 weeks of treatment respectively [135,136]. However, in the IXORA-R trial, ixekizumab showed a faster response versus guselkumab, although both drugs were comparable in terms of efficacy by week 24 [137].

Moreover, risankizumab showed superior efficacy versus ustekinumab with PASI 90 rates of 75.3 % and 74.8 %, respectively, at week 16 in the phase 3 UltIMMa-1 and UltIMMa-2 trials [138], while the NAVIGATE trial showed guselkumab's superiority in patients who did not respond adequately to 16 weeks of ustekinumab, achieving better Investigator Global Assessment scores [139]. Tildrakizumab achieved higher PASI 75 and PGA response rates than placebo at week 12, with continued improvement until week 28 in the reSURFACE 1 and 2 trials [140–142].

Recent evidence from both meta-analyses and real-world studies demonstrates the superior long-term persistence of IL-23 inhibitors. A comprehensive meta-analysis of 69 studies including 48,704 patients [143] found that IL-23 inhibitors, particularly risankizumab and guselkumab, achieved the highest summary drug-survival estimates for both overall and ineffectiveness-related persistence at 1, 2, and 3 years, significantly exceeding IL-17 inhibitors (secukinumab, ixekizumab, brodalumab) and all TNF-α inhibitors. A multicentre Italian IL PSO study [144] confirmed these findings in clinical practice, reporting the highest 4-year overall drug survival for risankizumab (91.6 %), followed by tildrakizumab (83.5 %) and guselkumab (82.4 %), with risankizumab also least likely to be discontinued for ineffectiveness (93.4 %). Similarly, in the BADBIR registry cohort [145], guselkumab and risankizumab demonstrated the most favourable adjusted 2-year survival times for both effectiveness (~1.93 years) and safety, outperforming IL-17A and TNF-α inhibitors. Collectively, these findings demonstrate the high rate of persistence and sustained therapeutic benefit of IL-23 blockade in PsO.

Table 1
Efficacy of IL-23 inhibitors in phase 3 RCTs in psoriasis patients.

Study	Design	Patients (n, setting)	Primary outcome	Results
IMMvent	Phase 3, RCT (risankizumab vs adalimumab)	n = 605, moderate-severe psoriasis	PASI 90 at wk16	Risankizumab 72 % vs adalimumab 47 %
UltIMMa-1 and UltIMMa-2 trials	Phase 3, RCT (risankizumab vs ustekinumab vs placebo)	n = 837, moderate-severe psoriasis	PASI 90 at wk16	Risankizumab 74.8–75.3 % vs ustekinumab 42–47.5 % vs placebo 2.0–4.9 %
VOYAGE 1	Phase 3, RCT (guselkumab (100 mg SC at weeks 0 and 4, then every 8 weeks) vs placebo/ adalimumab)	n = 506, moderate-severe psoriasis	PASI 90 at wk16	Guselkumab 73 % vs adalimumab 50 % vs placebo 3 %
VOYAGE 1	Phase 3, RCT (guselkumab vs placebo/ adalimumab)	n = 506, moderate-severe psoriasis	PASI 90 at wk48	Guselkumab 76 % vs adalimumab 48 % (placebo only 16 wks)
VOYAGE 2	Phase 3, RCT	n = 992, psoriasis	PASI 90 at wk16	Guselkumab 70 % vs placebo 2.4 %; sustained responses at wk48
ECLIPSE	Head-to-head RCT (guselkumab vs secukinumab)	n = 1048, psoriasis	PASI 90 at wk48	Guselkumab 84 % vs secukinumab 70 %
reSURFACE 1 and-2 trials	Phase 3, RCT (tildrakizumab vs placebo/ etanercept)	n = 772 for reSURFACE-1 and 1090 for reSURFACE2	PASI 75 at wk12	reSURFACE1; Tildrakizumab 62–64 %, placebo: 6 %. reSURFACE2; 61–66 %, etanercept: 48 %, Placebo: 6 %

PASI = psoriasis area severity index; RCT = randomised controlled trial; wk = week.

7. IL-23 as a therapeutic target in IBD

Several monoclonal antibodies targeting the IL-23p19 subunit have been developed and tested in clinical trials for IBD, showing substantial efficacy and safety profiles. These include risankizumab, guselkumab and mirikizumab. Results from clinical trials have demonstrated significant improvement in disease severity as well as improving patient quality of life (Table 2). In these trials, the primary endpoints were clinical remission defined by CD activity index (CDAI) or patient-reported outcome criteria [average daily stool frequency and abdominal pain score]) and endoscopic response at 12 weeks (induction timepoint) or one year (maintenance timepoint).

Risankizumab 600 mg has shown substantial benefit in patients with moderate-to-severe CD across multiple trials. In the ADVANCE study, at week 12 risankizumab led to 43 % stool frequency and abdominal pain score remission and 40 % endoscopic response, compared to 22 % and 12 % with placebo, while in the MOTIVATE study, risankizumab 600 mg resulted in 35 % clinical remission and 29 % endoscopic response versus 19 % and 11 % with placebo [19]. Patients responders to IV risankizumab induction, have been evaluated in the maintenance study Fortify [146]. Maintenance therapy with 360 mg risankizumab or 180 mg significantly improved stool frequency/abdominal pain remission (69.2 %, 64.1 % vs. 50.5 %), endoscopic response (70.2 %, 68.2 % vs. 38.4 %), and endoscopic remission (74.4 %, 45.5 % vs. 23.9 %) compared to placebo (withdrawal) and patients maintained durable clinical and endoscopic outcomes at one year [146].

Moreover, in a head-to-head study in TNF-IR patients, risankizumab was noninferior to ustekinumab for clinical remission at 24 weeks and had superior efficacy compared to ustekinumab at week 48 with respect to endoscopic remission [147]. Risankizumab was superior to ustekinumab also across all multiplicity-adjusted secondary end points, including clinical remission at week 48, endoscopic response at weeks 48 and 24, and glucocorticoid-free endoscopic remission and glucocorticoid-free clinical remission at week 48 [148].

Guselkumab has also shown efficacy in patients with CD. In the Galaxy 2 and 3 phase 3 trials, patients treated with guselkumab 100 mg SC q8w or 200 mg SC q4w achieved the co-primary endpoints (clinical response at week 12 and clinical remission/endoscopic response at week 48) relative to PBO. Moreover, at week 48, both guselkumab doses demonstrated superiority to ustekinumab for endoscopic response, endoscopic remission, deep remission and clinical remission and

Table 2
Efficacy of IL-23 inhibitors in phase 3 RCTs in patients with inflammatory bowel disease.

Study	Design	Population	Primary endpoints (timepoints)	Results
Risankizumab - ADVANCE	Phase 3, RCT (IV 600 mg induction)	Moderate-to-severe Crohn's disease (n = 1600)	Clinical remission (stool frequency + abdominal pain), endoscopic response - wk 12	43 % clinical remission and 40 % endoscopic response vs 22 % and 12 % placebo
Risankizumab - MOTIVATE	Phase 3, RCT (IV 600 mg induction)	Moderate-to-severe Crohn's disease (TNF-IR)	Clinical remission, endoscopic response - wk 12	35 % and 29 % vs 19 % and 11 % placebo
Risankizumab - FORTIFY	Phase 3, maintenance (SC 180 mg/360 mg q8w)	Responders to IV induction	Stool frequency/abdominal pain remission, endoscopic response and remission - wk 52	Clinical remission 64–69 %, endoscopic response 68–70 %, endoscopic remission 46–74 % vs 50 %, 38 %, 24 % placebo-withdrawal
Risankizumab vs Ustekinumab (H2H)	Phase 3b, active comparator (TNF-IR CD)	Moderate-to-severe Crohn's	Clinical remission wk 24; endoscopic remission wk 48	Noninferior to ustekinumab at wk 24; superior at wk 48 for endoscopic and clinical endpoints
Guselkumab - GALAXY 2 & 3	Phase 3, RCT (100 mg q8w/ 200 mg q4w SC)	Moderate-to-severe Crohn's disease (n ≈ 2400)	Clinical response wk 12; clinical/ endoscopic response wk 48	Met co-primary endpoints; superior to ustekinumab for endoscopic response, remission, deep remission, and combined outcomes
Guselkumab - Corticosteroid-sparing analysis	Sub-analysis of GALAXY trials	Moderate-to-severe Crohn's	Corticosteroid-free endoscopic response and remission wk 48	Endoscopic response 41–43 % vs 31 % ustekinumab; remission 28–30 % vs 20 % ustekinumab
Mirikizumab - Crohn's Disease Program	Phase 3, RCT	Moderate-to-severe Crohn's	Clinical remission, endoscopic response	Higher clinical remission and response vs placebo; noninferioto ustekinumab for clinical efficacy
Risankizumab - Ulcerative Colitis Induction/ Maintenance	Phase 3, RCT (IV 1200 mg induction → SC 180 mg/360 mg maintenance)	Moderate-to-severe ulcerative colitis	Clinical remission wk 12/wk 52	20 % vs 6 % placebo (wk 12); 40 % (180 mg)/38 % (360 mg) vs 25 % placebo (wk 52)
Guselkumab - Ulcerative Colitis Studies	Phase 3, RCT (IV 200 mg induction → SC 200 mg q8w)	Moderate-to-severe ulcerative colitis	Clinical remission wk 12/wk 24	Higher clinical remission vs placebo (wk 12); 77 % clinical response maintained to wk 24
Mirikizumab - LUCENT 1 & 2	Phase 3, RCT (300 mg q4w induction → maintenance for responders)	Moderate-to-severe ulcerative colitis	Clinical remission wk 12/wk 40	24 % vs 13 % placebo (wk 12); 50 % vs 25 % placebo (wk 40)

CD = Crohn's disease; UC = ulcerative colitis; PBO = placebo; UST = ustekinumab; TNF-IR = tumor necrosis factor inhibitor inadequate responders; wk = week.

endoscopic response [149]. Guselkumab showed better corticosteroid-sparing effects than ustekinumab at week 48 in patients with moderate to severely active CD. Guselkumab-treated patients achieved higher 90-day corticosteroid-free endoscopic response (guselkumab 100 mg q8w: 41.3 %, guselkumab 200 mg q4w: 42.5 % vs UST: 31.2 %) and endoscopic remission (guselkumab 100 mg q8w: 30.3 %, guselkumab 200 mg q4w: 28.3 % vs ustekinumab: 20.2 %), with greater overall corticosteroid-free outcomes [150]. Recently, approval has been granted for the use of mirikizumab in CD. Mirikizumab showed significantly higher clinical response and remission rates compared to placebo and non-inferior efficacy to ustekinumab, although not superior in endoscopic response [151]. Efficacy and safety of risankizumab, guselkumab and mirikizumab have been evaluated also in UC. Risankizumab 1200 mg outperformed placebo in achieving clinical remission at week 12 (20.3 % vs. 6.2 %) and clinical remission rates at week 52 were higher with risankizumab (40.2 % for 180 mg, 37.6 % for 360 mg) compared to placebo (25.1 %) [152]. In patients with moderate-to-severe UC, guselkumab 200 mg IV showed higher percentage of clinical remission vs. placebo at week 12 [153]. Continued treatment with guselkumab 200 mg SC through week 24 helped 77.2 % of patients to achieve clinical response. Patients with prior inadequate response to advanced therapy also benefited. Two phase 3 trials (LUCENT-1 and LUCENT-2) evaluated mirikizumab in adults with moderate-to-severe UC [154]. In the induction trial, patients received

Table 3
Efficacy of IL-23 inhibitors in phase 3 RCTs in patients with psoriatic arthritis.

Study	Design	Population	Primary endpoints (timepoints)	Results
PSUMMIT 1 & 2	Phase 3 RCT (ustekinumab vs placebo)	Active PsA (n = 615)	ACR20 wk 24	42–50 % vs 23 % placebo
DISCOVER-1	Phase 3 RCT (guselkumab 100 mg SC q4w or q8w; TNF-exposed allowed)	Adults with PsA (n = 381)	ACR20 wk 24	59 % (q4w), 52 % (q8w) vs 22 % placebo
DISCOVER-2	Phase 3 RCT (guselkumab 100 mg SC q4w or q8w; biologic-naïve)	Moderate-to-severe PsA (n = 741)	ACR20 wk 24	64 % (both q4w/q8w) vs 33 % placebo; improvements in enthesitis and dactylitis (45–50 % and 59–64 % vs 29 % and 42 % placebo)
DISCOVER-2 post-hoc	Long-term extension (100 weeks)	Biologic-naïve PsA	DAPSA-LDA and MDA wk 100	DAPSA-LDA 62 % (q4w) and 59 % (q8w); MDA 38 % and 40 % respectively; durable pain and spinal improvement
COSMOS	Phase 3b RCT (guselkumab 100 mg vs placebo)	PsA and IR-TNF (100 %) (n = 285)	ACR 20 wk 24	44.4 % vs 19.8 % placebo
KEEPsAKE-1	Phase 3 RCT (risankizumab 150 mg SC q12w; csDMARD-IR)	Active PsA (n = 964)	ACR20 wk 24 (primary); ACR50 and PASI90 wk 24 (secondary)	ACR20 57 % vs 33 % placebo; ACR50 33 % vs 11 %; PASI90 52 % vs 10 %; MDA 25 % wk 24, 38 % wk 52–100 (continuous therapy)
KEEPsAKE-2	Phase 3 RCT (risankizumab 150 mg SC q12w; csDMARD-IR and bDMARD-IR)	Active PsA (n = 444)	ACR20 wk 24	51 % vs 27 % placebo; ACR50 26 % vs 9 %; PASI90 55 % vs 10 %; MDA 33 % wk 100 (continuous therapy)
Tildrakizumab Phase 2	Phase 2 RCT (tildrakizumab 100 mg and 200 mg SC q12w)	Moderate-to-severe PsA (ñ400)	ACR20 wk 24	79 % (200 mg), 74 % (100 mg) vs 50 % placebo; favourable safety profile but no Phase 3 program completed

PsA = psoriatic arthritis; ACR = American College of Rheumatology response; MDA = minimal disease activity; DAPSA = Disease Activity index for Psoriatic Arthritis; IR = inadequate respomnse; LDA = low disease activity; PASI = Psoriasis Area and Severity Index; TNF = tumor necrosis factor; csDMARD = conventional synthetic disease-modifying antirheumatic drug; bDMARD = biologic DMARD; wk = week.

300 mg mirikizumab or placebo every 4 weeks for 12 weeks, followed by a maintenance trial for responders. Mirikizumab significantly improved clinical remission at weeks 12 (24.2 % vs. 13.3 %) and 40 (49.9 % vs. 25.1 %) compared to placebo.

8. IL-23 as a therapeutic target in PsA

The efficacy of risankizumab, tildrakizumab and guselkumab in PsA has been demonstrated in both phase 2 and phase 3 trials, however, to date, only risankizumab and guselkumab have been granted approval (Table 3) [132,155].

Efficacy and safety of risankizumab in patients with active PsA have been evaluated in the phase 3 clinical trials, KEEPsAKE-1 (included patients with inadequate response to csDMARDs (csDMARD-IR) [156] and KEEPsAKE-2 (included a mixed population, patients csDMARDs-IR and bDMARDs-IR) [157]; 57.3 % and 51.3 % of patients receiving 150 mg risankizumab achieved ACR20 at week 24, compared to 33.5 % and 26.5 % in the placebo groups, respectively. Furthermore, ACR50 response was higher in risankizumab groups, with 33.4 % and 26.3 % of patients achieving this outcome in KEEPsAKE-1 and KEEPsAKE-2, respectively compared to 11.3 % and 9.3 % in placebo groups, respectively.

In terms of improvement in skin symptoms, PASI90 responses were significantly better in risankizumab-treated patients at 24 weeks, with 52.3 % and 55.0 % of patients achieving PASI90 in KEEPsAKE-1 [156] and KEEPsAKE-2 [157], respectively, compared to 9.9 % and 10.2 % with placebo. Guselkumab (100 mg every 4 weeks or every 8 weeks) showed effectiveness in adults with PsA, both biologic-naïve and inadequate responders to anti-TNF. Data from the phase 3 DISCOVER-1 trial (biologic-naïve and inadequate responders to anti-TNF), indicated that at week 24, the primary endpoint ACR20 was achieved by 59 % in the 4-week group, 52 % in the 8-week group, and 22 % in the placebo group [17]. In DISCOVER-2 [18], 741 PsA patients biologic-naïve were randomized to guselkumab (every 4 or 8 weeks or placebo). At week 24, ACR20 was achieved by 64 % in both guselkumab groups, compared to 33 % in the placebo group. In both trials, guselkumab also showed benefits in physical functioning, enthesitis, dactylitis, and fatigue [17,18]. Pooled analyses revealed resolution of enthesitis in 45–50 % and dactylitis in 59–64 % of guselkumab-treated patients, compared to 29 % and 42 % in the placebo group [18]. In COSMOS, that included patients with inadequate response to anti-TNF treatment, 44.4 % of patients treated with 100 mg guselkumab achieved ACR 20 response at 24 weeks vs 19.8 % placebo [158]. At long-term (up to 100 weeks), both risankizumab and guselkumab showed maintenance of response. In the KEEPsAKE-1 trial, the percentage of patients achieving MDA at week 100 in the continuous risankizumab group was 38.2 %, which remained stable from week 52 (38.3 %) and was higher than at week 24 (25.0 %). In the placebo/risankizumab group, the percentage of patients achieving MDA increased at week 100 (35.2 %) compared to week 52 (28.0 %) and week 24 (10.2 %). In KEEPsAKE-2 up at 100 weeks the percentage of patients achieving MDA was 33.0 % in the continuous risankizumab group and 33.3 % in the placebo/risankizumab group, which was similar to week 52, where 27.2 % of patients in the continuous risankizumab group and 33.8 % of patients in the placebo/risankizumab group achieved MDA [159,160]. In a post-hoc analysis of DISCOVER-2 through 100 weeks [161], the DAPSA-LDA rates of 62 % with guselkumab every 4 weeks and 59 % every 8 weeks were observed. MDA was achieved in 38 % and 40 % of patients, respectively. Spinal pain and overall pain showed early reductions, with durable improvements sustained through week 100.

9. Safety profile of IL-23 inhibitors in psoriasis, IBD and PsA

Cumulative evidence from randomized control trials in psoriasis, IBD and PsA, demonstrates the favourable safety profile of IL-23 p19 inhibitors (Table 4). Listed safety warnings and precautions in guselkumab, tildrakizumab, and risankizumab SmPCs, include infections, hypersensitivity reactions, and tuberculosis (TB). Hepatotoxicity is

Table 4
Summary of key safety findings for IL-23 Inhibitors across psoriasis, inflammatory bowel disease and psoriatic arthritis.

Study/Reference	Design	Patients (n, setting)	Primary outcome	Main safety findings
Psoriasis				
UltIMMa-1 & 2, IMMvent, IMMhance, IMMerge Risankizumab	Phase 3 RCTs vs placebo, adalimumab, ustekinumab, secukinumab	>2000 adults with moderate-to-severe PsO	Efficacy (PASI 90/100) and safety	Well tolerated through 52 weeks; common AEs URTI, nasopharyngitis, headache; SAEs ≤3.5 %; no new IBD, TB, or MACE related to drug.
VOYAGE 1 & 2 NAVIGATE, ECLIPSE - Guselkumab	Phase 3 RCTs vs placebo, adalimumab, secukinumab	>2500 PsO	Efficacy and long-term safety	Overall multiple studies, rates of AEs were similar to placebo: Nasopharyngitis 7–25 %, URTI 3–16 %; AE rates comparable to placebo; 5-year pooled rates per 100 PY: serious infections 0.85, malignancy 0.45, non-melanoma 0.34, MACE 0.29.
reSURFACE 1 & 2 Tildrakizumab	Phase 3 RCTs vs placebo	1862 PsO	PASI 75, PGA response	Nasopharyngitis 4–14 %, injection-site erythema ≤9 %; no new or worsening IBD; favourable 5-year tolerability.
Inflammatory bowel disease				
ADVANCE, MOTIVATE (induction) & FORTIFY (maintenance) - Risankizumab	Phase 3 RCTs (CD, UC) vs placebo	>1500 CD/UC	Clinical remission and endoscopic response	AE rates similar to placebo; SAEs ≤13 %, serious infections 1–4 %; no MACE, malignancy, or deaths attributed to drug.
GALAXY 1 - Guselkumab	Phase 2b RCT (CD)	≈250	CDAI remission	AE ≤60 %; infections 12–18 % active vs 21 % placebo; SAEs 4–6 %; no opportunistic infections, TB, or deaths.
LUCENT 1 & 2 - Mirikizumab	Phase 3 induction + maintenance (UC)	≈1200	Clinical remission	AE rates similar to placebo; SAEs ≈5 %; opportunistic infections ~1 %; mild liver enzyme rise; no deaths; safety maintained to 104 weeks.
Psoriatic arthritis				
KEEPsAKE 1 & 2 - Risankizumab	Phase 3 RCTs vs placebo	>1400 PsA	ACR 20/50 responses	AEs ~40 %; SAEs 2–3 % vs 3–4 % placebo; serious infections ~1 %; no TB, IBD, or new safety signals to 148 weeks.
DISCOVER 1 & 2 - Guselkumab	Phase 3 RCTs vs placebo (q4w/q8w)	>1100 PsA	ACR 20/50 responses	SAEs ≤3 %; infection rates low; no IBD exacerbations or opportunistic infections; no deaths in active arms.
COSMOS Guselkumab	Phase 3b RCT (TNF-IR PsA)	~300	ACR 20 at 24 wks	SAEs 3.7 % vs 3.1 % placebo; no serious infections or deaths; mild URTI common; liver enzyme elevations rare; MACE/malignancy infrequent.

AE, adverse event; AEs, adverse events; AS, ankylosing spondylitis; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IL, interleukin; IBD-IR, inadequate responder to IBD therapy; IQR, interquartile range; MACE, major adverse cardiovascular event; n, number of patients; PGA, Physician's Global Assessment; PsA, psoriatic arthritis; PsO, psoriasis; PY, patient-years; q4w/q8w, every 4 or 8 weeks; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse event; SAEs, serious adverse events; SC, subcutaneous; SEC, secukinumab; TEAE, treatment-emergent adverse event; TNF, tumor necrosis factor; TNF-IR, tumor necrosis factor inhibitor-inadequate responder; UC, ulcerative colitis; URTI, upper respiratory tract infection.

listed for risankizumab and guselkumab in relation to the IBD indications [162–164].

In phase 3 trials, guselkumab 100 mg, risankizumab 150 mg, and tildrakizumab 100/200 mg showed consistent safety. Risankizumab was well tolerated up to week 52 in five trials (UltIMMa 1/2, IMMvent, IMMhance, IMMerge) [165], with common AEs being upper respiratory infections, diarrhea, and headache [138]. Serious or opportunistic infections, TB, malignancies, hepatic events, and MACE occurred in ≤3.5 % of patients, with no UC/CD cases [134]. AE profiles were consistent across studies, with no active/latent TB or severe hypersensitivity [166,167].

Guselkumab trials (VOYAGE 1/2, NAVIGATE, ECLIPSE) showed nasopharyngitis and URTI as most common AEs (3–25 %) [136,139,168,169]. Long-term follow-up up to 204 weeks confirmed low rates of serious infections, malignancies, and MACE [170]. In pooled VOYAGE 1/2 (7166 PY), serious infections, malignancy, and MACE rates were 0.29–0.85/100 PY, confirming sustained safety [171].

Tildrakizumab reSURFACE 1/2 demonstrated low AE rates (mainly nasopharyngitis, URTI, injection site erythema), with no new or worsening IBD [140]. Real-world studies confirmed favourable safety for IL-23 inhibitors [172–175].

In CD and ulcerative colitis (UC), IL-23 inhibitors maintained favourable safety.

Risankizumab induction and maintenance trials (ADVANCE, MOTIVATE, FORTIFY) showed AE rates similar to placebo, with SAEs in 4–13 % and serious infections <4 %; no MACE, malignancies, or deaths were reported [19,20]. In UC (INSPIRE, COMMAND), SAEs occurred in ≤5 % of risankizumab-treated patients vs 8–10 % with placebo [152]. Guselkumab (GALAXY 1) showed AE rates 42–50 % and infections 12–18 %, comparable or lower than placebo, with no TB or deaths [176].

Mirikizumab (VIVID-1, LUCENT-1/2/3) showed mild, balanced AE rates; liver enzyme elevations were rare and mostly mild [151,154,177,178]. Real-world studies of risankizumab in CD and UC confirmed low AE rates and good tolerability [179–181].

In PsA, risankizumab (KEEPsAKE-1/2) showed overall AEs in ~40 %, SAEs 2–3 %, serious infections ~1 %, with no new IBD or TB [156,157]. Long-term data (up to 148 weeks) confirmed stable safety [159,160,182]. Guselkumab (DISCOVER-1/2, COSMOS) showed low SAE rates (≤3 %), no serious infections or deaths, and mild nasopharyngitis or URTI [17,18,158]. AEs of special interest (MACE, malignancy, infection) were uncommon [183].

Meta-analyses have confirmed no significant difference in AEs or infections between IL-23 inhibitors and placebo, except for mild transaminase elevations (RR = 1.69; P < 0.001) [183,184]. Real-world data across psoriasis and PsA showed stable safety with low discontinuation rates and rare serious infections [185–187].

Although TB is an important concern in autoimmune-chronic inflammatory disease treatment, particularly with TNF inhibitors, IL-23 inhibitors have not demonstrated an increased risk of TB reactivation in clinical trials or real-world studies [188]. No active or latent TB cases were reported in major trials. Regardless, screening for latent TB remains vital before therapy, especially in TB-endemic regions, to ensure safe and appropriate treatment.

Taken together, IL-23 inhibitors demonstrate a favourable and consistent safety profile across several phase 2 and 3 clinical trials and real-world studies in psoriasis, IBD and PsA. AEs were generally mild to moderate, most commonly upper respiratory infections and nasopharyngitis, with serious infections, malignancies, and cardiovascular events remaining infrequent (<3–5 %) and not related to treatment. No significant new safety signals or cumulative toxicities emerged with long-term use (up to 5 years).

10. Perspectives on the use of IL-23 inhibitors in axPsA

Despite preclinical studies suggesting IL-23's role in axSpA, as previously mentioned, clinical trials evaluating the use of IL-23 and inhibitors in axSpA patients have been unsuccessful [100]. Consequently, the failure of IL-23 inhibitors in clinical trials for axSpA has raised important questions about the pathophysiological differences between spondyloarthritis. While IL-23 is increasingly recognised as being a key driver of inflammation in peripheral PsA and is successfully targeted in this setting, its role in axPsA and axSpA appears to be less clear. Potential reasons to explain this has been heavily debated [123,189,190].

Although these differences are not fully understood, the lack of efficacy emerged in axSpA is believed to stem from variations in the IL-23-responsive cell types involved and the timing of treatment [123]. It has also been suggested that axPsA is characterized by predominant ligament-centric inflammation, whereas AS primarily involves inflammation at the entheses [120]. This distinction may imply that the IL-23/IL-17 axis, a key pathway in peripheral joint inflammation, might not play the same role in axial disease.

A controlled trial is currently underway to evaluate guselkumab in patients with PsA and confirmed axial involvement (axPsA) through magnetic resonance imaging [191].

Moreover, it is worth highlighting that there is evidence, often derived from post-hoc analyses of registration trials, suggesting a response in the axial domain as well. A post-hoc analysis of the DISCOVER-1 and DISCOVER-2 studies found that guselkumab (every 4 or 8 weeks) significantly improved BASDAI and ASDAS scores in PsA patients with imaging-confirmed sacroiliitis (consistent with axial involvement), compared to placebo [192]. Improvements were seen by week 8, sustained through week 52, and were independent of HLA-B27 status. In KEEPsAKE 1 and 2 trials, risankizumab showed efficacy and safety in PsA patients up to 100 weeks [193]. Most patients who achieved minimal clinically important differences (MCID) in patient-reported outcomes at Week 24 maintained them through Week 100, including 86.4–100 % of placebo to risankizumab and 69.2–91.7 % of patients assigned risankizumab maintaining MCID in BASDAI across both trials.

Despite the negative results from axSpA trials, it remains possible that IL-23 inhibitors could be effective for a subset of patients with axPsA, especially if future studies identify biomarkers that distinguish IL-23-driven inflammation within axial disease. For now, however, international guidelines do not recommend the use of IL-23 inhibitors in axPsA due to the lack of supportive data [194,195].

11. Implications of IL-23 centrality in "skin-joint axis" for transition from psoriasis to PsA as well as the "gut-joint axis" for transition from gut to joint in PsA

Several studies have specifically estimated the prevalence of psoriasis, PsA and IBD and subpopulations with two or more of these overlapping diseases [196–210] (Fig. 2). It is recognised that about one-third of patients with psoriasis will go on to develop PsA [200–204]. Indeed, a number of studies have specifically focussed on identifying potential risk factors that may be linked to the development of PsA from psoriasis [211–215]. Data derived from several studies suggest that no single variable can reliably predict the transition to synovio-entheseal disease. Instead, this progression is driven by a complex interplay of multiple factors [214,216].

Several processes have been proposed to explain potential mechanisms involved in the development of PsA [216]. One process suggests that chronic skin inflammation spreads to synovio-entheseal tissues, via migration of IL-23 T cells, leading to systemic effects [96,216,217]. Another process proposed is that factors promoting musculoskeletal inflammation are present in extra-cutaneous areas, such as the gut mucosa or entheses [100,216,218].

A third theory proposes that PsA is an autoimmune condition triggered by an unidentified self-antigen [219,220]. Lastly, it is believed that all psoriasis patients have the potential to develop PsA, but only about 30 % transition to PsA [200–204] due to a failure in suppression

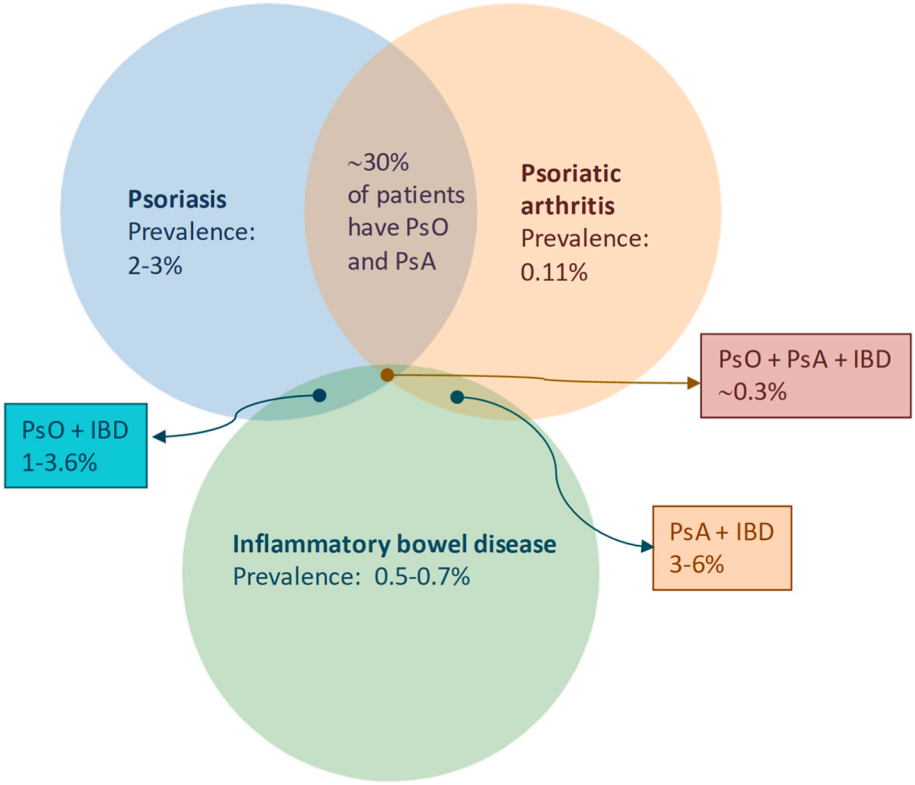

Fig. 2. Association between psoriasis, psoriatic arthritis and inflammatory bowel disease. IBD = inflammatory bowel disease, PsA = psoriatic arthritis, PsO = psoriasis. Prevalence of PSO of 2–3 % [196], PsA of 0.11 % [197], IBD of 0.5–0.7 % [198,199], PsO + PsA of 25–41 % (~30 %) [200–204], PsO + IBD of 1–3.6 % [204–207], PsA + IBD of 3–6 % [208,209] and all three (PSO + PSA + IBD) of ~0.3 % [210].

mechanisms, particularly the role of regulatory T cells [221–223]. More recently, a retrospective study evaluated the risk of developing PsA in plaque psoriasis patients treated with different biologics (TNF, IL-17, IL-23 inhibitors) [224]. Among 622 patients, those receiving IL-17 or IL-23 inhibitors had a lower risk of developing PsA compared to TNF inhibitors. After adjustment, hazard ratios for IL-17 and IL-23 were 0.63 and 0.57, respectively. Therefore, patients treated with IL-17 or IL-23 inhibitors have a lower risk of developing PsA compared to those treated with TNF inhibitors.

Each of these processes involves the activation of TNF and IL-23–IL-17 inflammatory pathways. The preclinical stage is marked by abnormal immune activation, particularly through the IL-23–IL-17 axis and TNF, driven by stimuli originating from the skin, gut microbiome, or entheses [7,23,96,100,216]. Following this is a subclinical stage, where biomarkers and musculoskeletal changes are detectable using imaging methods such as MRI and musculoskeletal ultrasonography [225–230]. A brief period of joint pain and fatigue then occurs before the onset of clinically apparent PsA [216,230–232].

Data from retrospective cohort studies suggest that psoriasis receiving biological treatment reveal a significantly lower risk of developing PsA vs. patients treated with phototherapy, topical/no treatment or no biological treatment [233–236].

In a retrospective study including 464 patients without PsA at enrolment, the incidence of PsA in patients with moderate-to-severe plaque psoriasis undergoing either continuous biological disease-modifying antirheumatic drugs (bDMARDs) treatment or phototherapy was investigated [237]. The annual incidence rate of PsA was lower in the bDMARDs group (1.20 cases per 100 patients/year) compared to the phototherapy group (2.17 cases per 100 patients/year), with an adjusted hazard ratio (HR) of 0.27. Older age, nail psoriasis, and longer psoriasis duration increased PsA risk. Overall, bDMARDs treatment reduced PsA risk [237].

Another retrospective study using the TriNetX database included 15,501 adult patients with psoriasis in the USA. These patients had been newly prescribed biologics, specifically TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, or IL-23 inhibitors, following initial diagnosis of psoriasis [234]. Singla and colleagues observed that 6.3 % of the patients developed inflammatory arthritis, with an incidence rate of 2.6 cases per 100 person-years.

Patients treated with IL-23 inhibitors or IL-12/23 inhibitors had a significantly lower risk of developing inflammatory arthritis compared to those receiving TNF inhibitors (adjusted hazard ratios; HR) for IL-12/23 inhibitors were 0.58, and 0.41 for IL-23 inhibitors).

There was no significant risk reduction observed for IL-17 inhibitors compared to TNF inhibitors. A further retrospective study based on the global Trinetx global database including almost 200 million patients compared the incidence of PsA among psoriasis patients receiving different biological treatments [236]. IL12/23 and IL-23 significantly reduced the risk of developing PsA compared to TNF and IL-17 inhibitors, both in first-line and second-line treatments in 5-year follow up. These findings revealed that IL-12/23 and IL-23 significantly reduce the risk of PsA compared to TNF inhibitors and IL-17 inhibitors, in both treatment-naïve and bio-experienced patients.

In another retrospective population-based analysis, the risk of developing inflammatory arthritis in psoriasis patients treated with biologic therapies was analyzed [235]. Data from 2007 to 2023 showed that patients receiving IL-23 inhibitors had a lower risk of developing arthritis compared to those treated with IL-17 and TNF inhibitors. Incidence rates were 4.99 for IL-23, 7.29 for IL-17, and 9.39 for TNF inhibitors (per 100 person-years). These findings show that patients receiving IL-23 inhibitors are at lower risk for developing inflammatory arthritis or PsA compared to those receiving IL-17 and TNF inhibitors.

Despite these promising results, the study's retrospective nature introduces potential biases, such as protopathic bias and confounding by indication [238]. Thus, while these findings suggest a role for IL-12/23 and IL-23 inhibitors in reducing arthritis risk, further prospective studies

with detailed risk stratification are necessary to confirm their efficacy in preventing the transition from psoriasis to psoriatic arthritis [238]. While data from case series focusing on the "subclinical PsA" stage, showing the possibility to "reverse" such a phase (with improvement/remission of arthralgia and/or synovio-entheseal inflammation on imaging) are indeed important [239], prospective controlled trials with larger sample size are needed to confirm these preliminary results. To address, this the PAMPA study is currently evaluating the efficacy of guselkumab in preventing PsA and reducing musculoskeletal abnormalities in psoriasis patients at high risk for PsA for the presence of subclinical inflammation detected by ultrasound [240].

There is also emerging evidence to support a "gut-joint axis," in SpA, including PsA, in which IL-23 produced within intestinal tissues activates tissue-resident lymphocytes and innate-like T cells (including Th17 and ILC3 populations), that may subsequently migrate to joint and entheseal sites [241–244].

These IL-23–responsive resident cells, originally primed in the gut, can sustain chronic IL-17 production after homing to the synovio-entheseal complex, thereby bridging mucosal and articular inflammation. Experimental models have shown Th17 cells and ILC3s are elevated in both gut and joint environments [23,59,73,245], this commonality suggests a shared pathogenic pathway where immune responses in the gut may prime systemic inflammation, affecting peripheral sites such as joints. Indeed, TRM-T cells and ILC3s are now recognised as key mediators maintaining inflammatory "imprints" that can be reactivated upon IL-23 stimulation [242].

Several studies have highlighted the similarity in the inflammatory profiles of the intestine and joints in SpA patients [241,246]. Both tissues exhibit an increased presence of pro-inflammatory cytokines, including IL-17 and IL-23, which are pivotal in driving inflammation.

Furthermore, it was observed that innate-like T cells can be skewed toward a predominant pro-inflammatory state [247]. These immune cells may migrate from the gut to the joint, perpetuating inflammation [248].

It has also been proposed that dysbiosis, or imbalance in the gut microbiota, may trigger the aberrant immune responses seen in SpA [242,249]. Alterations in gut microbiota composition can lead to increased intestinal permeability, allowing microbial products to translocate into the bloodstream, activating immune cells and contributing to systemic inflammation [250,251]. Mechanistically, short chain fatty acids derived from microbiotal fermentation play a key role in the immunometabolic regulation of intestinal type 17 and Treg cells thus regulating the IL-23/17 axis [252–254]. This gut-derived inflammation may then serve as a precursor to joint inflammation, providing a mechanistic link between the gut and joint pathologies observed in SpA.

Supporting this hypothesis, Ciccia and colleagues analyzed the levels of ILC1, ILC2, and ILC3 cells in ileal and bone marrow biopsies, as well as in peripheral blood and synovial fluid mononuclear cells from both AS patients and controls [255]. Their findings revealed that IL-17+ and IL-22+ ILC3 cells originating from the gut are increased in the peripheral blood, synovial fluid, and inflamed bone marrow of AS patients. This suggests an active homing pathway between the gut and inflamed sacroiliac joints.

The role of the inflammasome is also an area of interest that may help explain the gut-joint axis. Inflammasomes are innate immune system receptors and sensors that control the inflammatory response and coordinate antimicrobial host defences [256] and their activation can induce the release of IL-23 and IL-17 in human mononuclear cells [257].

Furthermore, Guggino and colleagues demonstrated for the first time that inflammasome activation occurring in rodent models and AS patients is associated with dysbiosis, and is involved in triggering ileitis in SKG mice [258]. The Inflammasome drives type 3 cytokine production with an IL-1β-dependent mechanism in AS patients.

Recent studies based on Mendelian randomization analysis have also provided important clues in our understanding of the pathogenic link between the gut and development of PsA. Gut microbiota significantly influences inflammatory arthritis, including PsA [11,259,260]. Evidence from epidemiological studies also highlight a link between PsA and gut microbiota, especially through its association with IBD, which affects joint symptoms in about one-third of IBD patients [261,262]. Dramatic alterations in gut microbiota are observed in IBD [263], and some studies suggest its role in psoriatic bone remodeling, even without arthritis symptoms [264]. Additionally, microscopic intestinal lesions are often found in PsA patients, even in the absence of intestinal symptoms [265].

Recently, a two-sample Mendelian randomization analysis was conducted using data from 13,266 gut microbiota samples and 3186 PsA patients [266]. The study revealed that bacteria like Rikenellaceae and Ruminococcaceae UCG011 negatively affected PsA, while Methanobacteria and Eubacterium fissicatena were found to be protective. These findings suggest that alterations in the gut microbiota may influence the risk and severity of PsA. In summary, the similarities between intestinal and joint inflammation in SpA, including PsA, suggest a pathogenic sequence where gut inflammation precedes and contributes to joint inflammation.

12. Clinical implications

An awareness of the clinical features and therapeutic applications of IL-23 inhibition across immune-mediated diseases, including psoriasis, PsA, and IBD, is essential for understanding the evolving role of this pathway in precision treatment strategies.

Selective inhibition of the IL-23 (p19) subunit has been show to demonstrate superior efficacy compared with dual IL-12/23 (p40) blockade. Clinically, risankizumab and guselkumab have shown higher rates of skin clearance and joint response than ustekinumab in psoriasis and PsA [138,156,168,192,267–269]. These findings position IL-23 (p19) inhibitors as preferred agents within the therapeutic armamentarium.

The therapeutic schedule of IL-23 inhibition varies by disease (See Table 5). In PsA, guselkumab every 4 weeks can yield slightly greater joint responses than every 8 weeks [126]. In IBD, an intravenous induction phase (e.g., risankizumab 600 mg at weeks 0, 4, and 8) followed by subcutaneous maintenance dosing is both effective and well tolerated [19,270]. By contrast, tildrakizumab is currently only approved for psoriasis [142,271], emphasizing the need to tailor therapy to organ involvement.

IL-23 inhibitors demonstrate broad therapeutic activity across the skin, joints, and gut, supporting a unified pathogenic model of IL-23–driven immune-mediated inflammatory disease. Clinical trials such as DISCOVER-2 [267] and ADVANCE/MOTIVATE [19] confirm improvements in both articular and intestinal endpoints, emphasizing their capacity to address multisystem disease.

Emerging data suggest early IL-23 blockade may prevent disease progression. The phase 3 GUIDE study demonstrated that sustained IL-23 inhibition can suppress tissue-resident memory cells, potentially altering the chronic inflammatory trajectory of psoriasis [272]. Further analyses in GUIDE will assess the relationship between disease memory (represented by TRM and regulatory T cell/Th17 cell frequencies) and clinical response. Observational studies further suggest reduced risk of PsA development among psoriasis patients treated with IL-23 or IL-12/23 inhibitors compared with TNF blockers [224,236].

IL-17 can be produced independently of IL-23 via innate-like lymphocytes including MAIT cells, γδT cells, and ILC3s, potentially explaining residual inflammation in some IL-23–resistant phenotypes [39–41]. Recognition of these alternative pathways is important for clinical decision-making and supports the development of precision strategies combining IL-23 and IL-17 pathway modulation.

13. Conclusion

IL-23 is a pivotal cytokine in the pathogenesis of psoriasis, PsA, and

Table 5
Dosing and administration schedule of IL-23 inhibitors in psoriasis, IBD and psoriatic arthritis.

Disease	Drug	Dose & administration schedule
Psoriasis (Plaque)	Risankizumab	150 mg SC at weeks 0, 4 then every 12 weeks
	Guselkumab	100 mg SC at weeks 0, 4, then every 8 weeks
	Tildrakizumab	100 mg SC at weeks 0, 4, then every 12 weeks
IBD (Crohn's Disease)	Risankizumab	Induction: 600 mg IV induction at weeks 0, 4, and 8 then maintenance: 180 or 360 mg SC every 8 weeks, starting at week 12
	Guselkumab	Induction with 400 mg SC at weeks 0, 4 and 8 (given as two 200 mg injections each time) or 200 mg (IV) at the same time points, followed by maintenance with either 200 mg SC every 4 weeks starting at week 12 or 100 mg SC every 8 weeks starting at week 16.
	Mirikizumab	900 mg (3 vials of 300 mg each) by IV infusion for at least 90 min at 0, 4 and 8 weeks and maintenance 300 mg SC every 4 weeks
IBD (Ulcerative Colitis)	Risankizumab	Induction: 1200 mg IV at weeks 0, 4, and 8. Maintenance: 180 mg or 360 mg SC every 8 weeks, starting at week 12.
	Guselkumab	Induction with 400 mg SC at weeks 0, 4 and 8 (given as two 200 mg injections each time) or 200 mg (IV) at the same time points, followed by maintenance with either 200 mg SC every 4 weeks starting at week 12 or 100 mg SC every 8 weeks starting at week 16.
	Mirikizumab	300 Induction: 300 mg IV every 4 weeks at weeks 0, 4, and 8 for at least 30 min. Maintenance: 200 mg SC every 4 weeks, starting at week 12.
Psoriatic Arthritis	Risankizumab	150 mg SC at weeks 0, 4 then every 12 weeks
	Guselkumab	Induction: 100 mg SC at weeks 0 and 4 and then maintenance: 100 mg (SC) every 8 weeks thereafter.
	Tildrakizumab	Not yet approved. Recommended: 100 mg as a SC injection at 0 and 4 weeks and once every 12 weeks thereafter

Recommended dosing/administration schedules according to product information leaflet. IV = intravenous; SC = subcutaneous.

IBD. In psoriasis, IL-23 stimulates keratinocyte proliferation and perpetuates chronic skin inflammation. In PsA, it drives joint and periarticular inflammation, leading to bone erosion and pathological new bone formation. Similarly, in IBD, IL-23 orchestrates intestinal inflammation, contributing to structural damage and disease progression.

Pivotal phase 3 trials and real-world studies have consistently demonstrated the efficacy and safety of IL-23 inhibitors across psoriasis, PsA, and IBD. Recent data further highlight their sustained therapeutic benefits, establishing IL-23 inhibitors as potential first-line biologic agents in these conditions.

These findings clearly illustrate the life-changing impact of IL-23 inhibitors in reducing disease burden and improving patient outcomes. IL-23 plays a central regulatory role in the complex interplay between the skin, gut, and joints. As research progresses, unraveling the interconnections mediated by IL-23 provides critical insights into shared inflammatory pathways, opening new avenues for innovative therapies.

Early intervention with IL-23 inhibitors shows promise as an effective strategy to prevent disease progression. Treatments such as risankizumab (approved for psoriasis, PsA, and IBD) and guselkumab (approved for psoriasis, PsA, UC and CD) offer significant advances in the management of these IMIDs, improving quality of life and addressing the multifaceted challenges of chronic inflammation.

CRediT authorship contribution statement

Alen Zabotti: Writing – review & editing, Writing – original draft. **Lucia Novelli:** Writing – review & editing, Writing – original draft, Conceptualization. **Michele Maria Luchetti Gentiloni:** Writing – review & editing, Writing – original draft. **Giuliana Guggino:** Writing – review & editing, Writing – original draft, Conceptualization. **Ana Biljan:** Writing – review & editing, Writing – original draft, Conceptualization. **Ennio Lubrano:** Writing – review & editing, Writing – original draft, Conceptualization. **Dennis McGonagle:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

Alen Zabotti: Honoraria for speaking with: AbbVie, Lilly, Novartis, UCB, J&J; research support/grant: J&J. Lucia Novelli: employed by AbbVie and may own AbbVie stocks/stock options. Michele Maria Luchetti Gentiloni: Research support from AbbVie; consulting fees from AbbVie, Janssen, Novartis, and Pfizer; speaker fees from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, and Pfizer. Giuliana Guggino: No conflict of interest to declare. Ana Biljan: employed by AbbVie SrL and may own AbbVie stocks/stock options. Ennio Lubrano: Honoraria for speaking with: AbbVie, Lilly, Novartis and UCB. Dennis McGonagle: has received honoraria or consultation fees from AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, UCB; grants/research support for AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, UCB, Lilly; participation in speaker's bureau for AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer and UCB.

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Data availability

No data was used for the research described in the article.

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