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IL-23 orchestrating immune cell activation in arthritis

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Abstract

IL-23 is a cytokine member of the IL-12 superfamily. These heterodimeric cytokines offer broad immune regulatory activity with potential effector function in inflammatory arthritis. IL-23 is a pro-inflammatory cytokine secreted by dendritic cells and macrophages. It plays a key role in both innate and adaptive immunity. By promoting and maintaining T cell differentiation into Th17 T cells, IL-23 is a key player in the pathogenesis of rheumatic diseases. Data from pre-clinical IL-23 knockout models show the major importance of IL-23 in development of arthritis. The induction and maintenance of type 17 cells, which secrete IL-17A and other pro-inflammatory cytokines, contributes to local synovial inflammation and skin inflammation in PsA, and perhaps in RA. Commensurate with this, therapeutic strategies targeting IL-23 have proven efficient in PsA in several studies, albeit not yet in RA.

Key words: IL-23, interleukin 23, arthritis, inflammation, cytokines, immunity

Rheumatology key messages

- IL-23 is a cytokine belonging to the IL-12 family secreted by dendritic cells and macrophages.
- IL-23 plays a key role in arthritis initiation by acting as a regulator of Th17 differentiation and IL-17 secretion.
- The IL-23–IL-17 axis plays a crucial role in psoriatic arthritis and spondylarthritis pathogenesis.

SUPPLEMENT

IL-12/23 superfamily structure and receptor system

Across the broad landscape of cytokines implicated in the pathogenesis of disease, the IL-12 family is remarkable. The heterodimeric structure of the members of this family confers upon them specific functional activities across a range of leucocyte subsets, and hence broad immune-regulatory potential. In addition, the IL-12 family belongs to the IL-6 superfamily and hence shares structural characteristics with IL-6 related cytokines. IL-12 cytokines are composed of an α-chain (p19, p28 or p35) and a β-chain [p40 or Epstein–Barr virus-induced molecule 3 (Ebi3)]. The α-chain shares a four helix bundle structure with the IL-6 superfamily, while the β-chain is structurally homologous to soluble class I cytokine receptor chains, such as IL-6 receptor-α [1]. As distinct from IL-12, which is composed of a dimer of both p40 and p35 chains, IL-23 comprises an association of p40 and p19 chains [2]. In addition, Ebi3 pairs with p28 to form IL-27 or with p35 to form IL-35, the latest-discovered member of the family [3, 4]. For these, however, there remains some doubt as to their structural integrity *in vivo*. IL-12 family cytokines also share their receptor subunits: IL-12 receptor (IL-12R) is a dimer of IL-12Rβ1 and IL-12Rβ2, while IL-23 signals through IL-12Rβ1 and IL-23 receptor (IL-23R). In contrast, IL-27 and IL-35 use gp130 in common with the IL-6 family and WSX-1 or IL-12Rβ2, respectively [5]. The p40 subunit of IL-23 binds to the IL-12Rβ1 and p19 to the IL-23R chain, inducing receptor oligomerization. Downstream signalling is mediated by members of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) family. Phosphorylation of STATs occurs through JAK2, along with JAK1 or tyrosine kinase 2 (TYK2). IL-23R is associated with phospho (p)STAT3 and pSTAT4 while IL-12R signalling is mediated via pSTAT4 [6, 7]. The molecular pathways associated with IL-12/IL-23 signalling are primarily associated with immune regulation. IL-12 family members along with their receptors are presented in Fig. 1.

Role of IL-23, compared with other family members, in the innate and adaptive immune systems

All IL-12 family cytokines play a role in immune response regulation. As distinct from IL-12 and IL-23,

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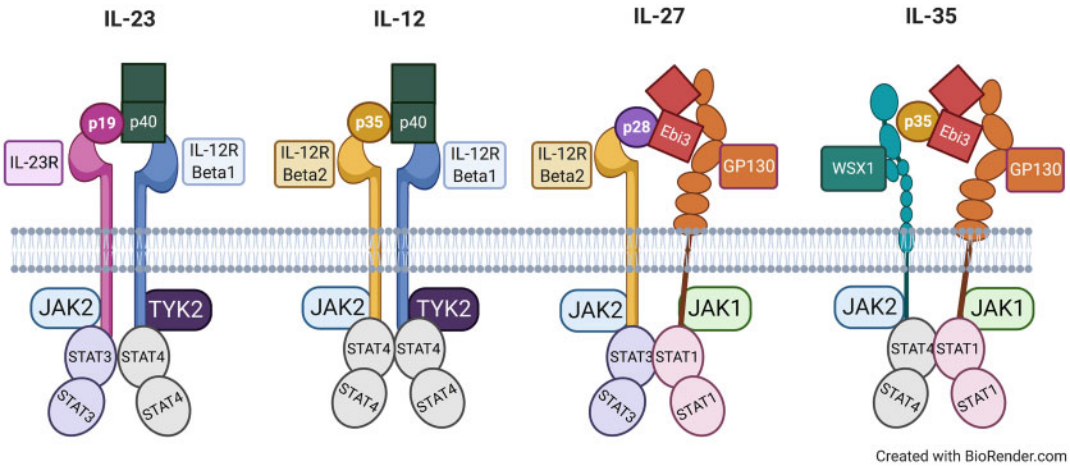
Fig. 1 IL-12 superfamily members and receptors



Ebi3: Epstein–Barr virus-induced molecule 3; IL-12R: IL-12 receptor; IL-23R: IL-23 receptor; JAK: Janus kinase; STAT: signal transducer and activator of transcription; TYK2: tyrosine kinase 2.

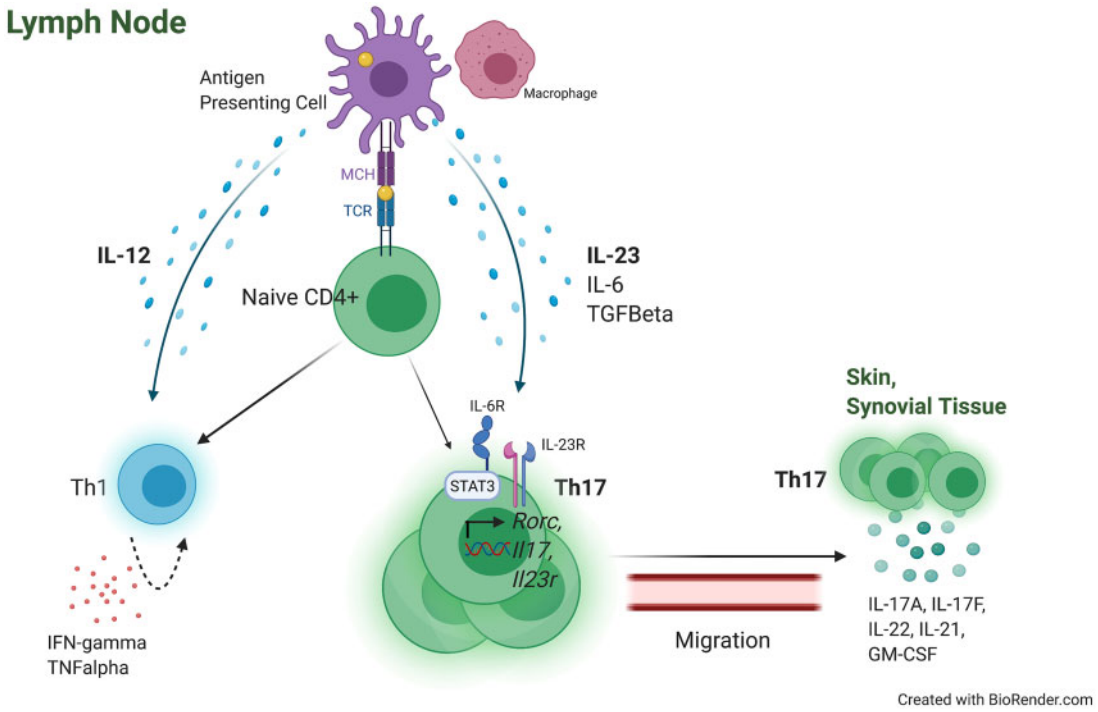
which are predominantly pro-inflammatory cytokines, IL-35 appears to act as a tolerance inducer through the enhancement of the T regulator cell population whereas IL-27 can play both pro- and anti-inflammatory roles dependent upon context, ambient cytokine concentrations and cellular maturity [4, 8]. IL-23R is expressed by different cell types including macrophages, dendritic cells and natural killer (NK) cells, and IL-23 is mainly expressed by dendritic cells and monocytes. IL-23 plays an important role in driving innate immune responses in the context of infectious diseases. For instance, IL-12 and IL-23 have been shown to drive NK responses and intrinsic immune memory against different pathogens such as *Toxoplasma gondii* [9]. IL-23 also acts as a mucosal immune defence enhancer, by co-stimulating mucosally associated T cells and participating in gut barrier homeostasis [10, 11]. In addition, genetic studies have demonstrated increased susceptibility to *Salmonella* and *Mycobacterium* in *IL12B* or *IL23BR1* variant carriers, suggesting an important role of IL-23 in host defence [12].

The differentiation of naïve T cells into effector cells is largely mediated by the cytokine environment shaped by antigen presenting cells especially dendritic cells. IL-12 is a pro-inflammatory cytokine acting as a determinant of naïve CD4 and CD8 positive T lymphocyte differentiation, during initial encounter with an antigen, into a population of Th1-cells capable of producing large amounts of IFN-γ following activation. In addition, IL-12 enhances the secretion of IFN-γ by differentiated Th1 cells during antigen responses and stimulates the development of IFN-γ-producing Th1 cells from the resting memory T cells subsets [13, 14]. Of interest, although structurally related, IL-23 does not trigger a Th1 response, but rather drives T lymphocyte differentiation into a Th17 phenotype [15, 16].

The Th17 lineage is characterized by the expression of a specific gene signature including the transcription factor RORγt, and cytokines such as IL-17A, IL-17F, IL-22, TNF and IL-21. IL-17A has an important role in orchestrating tissular inflammation in several auto-immune or inflammatory diseases such as PsA [17, 18]. The IL-17 family consists of six members (IL17A, B, C, D, E and F). IL-17A and F are prominently involved in auto-immune diseases and can be secreted as homodimers or as an IL-17A–IL-17F heterodimer. Consequent on the foregoing, whereas IL-12 was originally considered as the main trigger of auto-immune phenomena in several diseases, *in vivo* studies using murine models of both multiple sclerosis (experimental autoimmune encephalomyelitis) or arthritis [collagen-induced arthritis (CIA)] revised this by showing the prominent role of the IL-23–IL-17 axis over the IL-12–IFN-γ pathway in the development of auto-immunity [15, 19].

Of interest, TGF-β in the presence of pro-inflammatory cytokines, mainly IL-6, promotes Th17 differentiation. IL-6 acts as a key driver of Th17 differentiation through induction of specific genes from the Th17 lineage such as *Rorc*, *Il17* and *Il23r* via STAT3 activation [20], which also inhibits TGFβ-induced forkhead box P3 expression subsequently inhibiting the differentiation of Treg cells [21]. However, it is important to note that Th17 cells induced by IL-6 and TGF-β display a weak pathogenic phenotype and are unable to drive auto-immune diseases [22, 23]. In addition, although IL-23 alone is unable to prime the differentiation of naïve $CD4^+$ cell into Th17 cells, its contribution to the maintenance of the Th17 pathogenic phenotype though enhanced inflammatory functions is well established [21, 24]. More specifically, IL-23 promotes maintenance of Th17 signature genes (*Rorc* and *Il17*) and effector genes (*Il22, Csf2* and *Ifng*) while using a feedback loop to amplify the signal through the upregulation of *Il23r* expression and downregulation of inhibiting factors such as IL-2, IL-27 and IL-12. These elements are summarized in Fig. 2.

FIG. 2 Role of IL-23 and IL-12 on T cell differentiation in arthritis



STAT: signal transducer and activator of transcription.

IL-23 in rheumatic diseases: what can we learn from animal models?

The first demonstration of the role of IL-23 in an experimental model of arthritis strongly contributed to a better understanding of its role. As an example, IL-23p19-deficient (*Il23a*$^{-/-}$) mice were protected against the development of CIA since mice lacked functional IL-23 and therefore the Th17 cell subset, whereas the Th1 compartment was not altered [19]. Logically, synovial levels of IL-17 were reduced but also other pro-inflammatory cytokines such as TNF, IL-6 and IL-1β. Conversely, knockout of IL-12 in mice (*Il12a*$^{-/-}$) was not able to prevent the development of arthritis and in fact exacerbated arthritis. These data emphasized the important role of IL-23 at the early stage of arthritis [25]. Similarly, total IL-17 (*Il17*$^{-/-}$) deficient mice were protected against arthritis while the incidence of arthritis in mice deficient selectively for IL-17A was reduced to 20% [26]. Importantly, some studies also highlighted the potential of IL-23 to trigger osteoclastogenesis. As an example, Yago *et al.* demonstrated that IL-23 was able to induce osteoclast (OC) differentiation in peripheral blood mononuclear cells in the absence of receptor activator of nuclear factor κB (RANK) ligand (RANKL). Subsequently, blockade of IL-23 activity by anti-IL-23p19 antibody at an early stage of disease could attenuate CIA in rats by preventing both inflammation and bone destruction [27]. Further investigation of IL-23 blockade's effect across the course of arthritic disease showed that use of anti-IL-23p19 antibody could suppress significantly disease severity in CIA model if administered 15 days before clinical signs of disease onset, while IL-23 neutralization at a later stage of the disease was proven inefficient [28].

Another study described an indirect influence of IL-23 on auto-antibody formation and inflammatory activity and glycosylation profile through the promotion of Th17 cell differentiation in an IL-21 and IL-22 dependent manner [29]. Activated Th17 will act at both lymph node and synovium sites influencing plasma cell differentiation through the regulation the expression of β-galactoside α2,6-sialyltransferase thereby determining the glycosylation profile and activity of IgG.

To assess the role of IL-23 in non-autoimmune arthritis models, the methylated BSA (mBSA) antigen induced arthritis (AIA) model [30] was applied in IL-23p19-deficient and IL-17 receptor A (IL-17RA) knockout mice. Of interest, *Il23*$^{-/-}$ mice displayed a milder arthritic phenotype associated with consequent reduction of structural damage. Additionally, Th17 and IL-17^{+} γδ T cell subsets were significantly reduced, highlighting the role of the IL-23–IL-17 axis in disease initialization and severity.

Further studies explored the role of IL-23 in arthritis induction in other rodent immune disease models, showing that the transfection of an adenoviral vector encoding a single-chain of IL-23 in non-obese diabetic mice led to the development of skin lesions compatible with psoriasis, intervertebral disc degeneration, synovial

Table 1 Role of IL-23 in arthritis development and severity: data from pre-clinical models

Reference	Mouse and arthritis model	IL-23 expression	Effect
Murphy *et al.* [19]	Mouse CIA model	IL-23p19-deficient (*Il23a*$^{-/-}$) mice	No arthritis
Yago *et al.* [27]	Rat CIA model	Anti-IL-23p19 antibody	Prevention of both inflammation and bone destruction
Cornelissen *et al.* [28]	Mouse CIA model	Anti-IL-23p19 antibody	Reduction of disease severity if administered 15 days before clinical signs of disease onset, but not after
Pfeifle *et al.* [29]	CIA model, K/BxN arthritis	IL-23p19-deficient (*Il23a*$^{-/-}$) mice	No arthritis in CIA; arthritis of equal severity in wild-type mice and *Il23a*$^{-/-}$ mice with passive transfer of serum from arthritic K/BxN mice
Cornelissen *et al.* [30]	Mouse AIA model	IL-23p19-deficient (*Il23*$^{-/-}$) mice	Milder arthritic phenotype, reduction of structural damage
Flores *et al.* [31]	NOD mice	Adenoviral vector encoding a single-chain of IL-23	Skin lesions compatible with psoriasis, intervertebral disc degeneration and synovial hypertrophy and cartilage
Sherlock *et al.* [32]	B10.RIII mice	IL-23 overexpression by hydrodynamic delivery of an IL-23 minicircle	Development of enthesitis and entheseal new bone formation

CIA: collagen-induced arthritis; AIA: Methylated BSA antigen-induced arthritis, NOD: Non-obese diabetic.

hypertrophy and cartilage loss [31]. In addition, the role of IL-23 overexpression in driving spondyloarthritis in the CIA-antibody-induced arthritis model was described by Sherlock *et al.* [32]. More specifically, characteristic development of enthesitis and entheseal new bone formation was observed, therefore illustrating the role of IL-23 in enthesis involvement in spondylarthropathy. These data are summarized in Table 1.

Roles of IL-23 in activating relevant cell types across the range of human inflammatory arthropathies

Since pre-clinical models suggested an important role in arthritis initiation and persistence, translational studies have also evaluated the role of IL-23 in human rheumatic diseases such as RA and PsA. Studies can be usefully separated across different disease stages. Regarding arthritis initiation, Pfeifle *et al.* reported an inflammatory antibody profile both in people with ACPA positive RA and in people at risk of arthritis expressing ACPA without clinical symptoms, suggesting that IL-23 could contribute to the breach of tolerance against citrullinated peptides at a preclinical stage of the disease [29].

During the established stage of RA, clinical studies have shown increased serum levels of IL-23 in RA patients *vs* healthy controls. However, in this study the levels of IL-23 were not correlated with disease activity or other clinical aspects [33] and the pathogenetic link is uncertain on this basis. IL-23p19 subunit expression was also increased in both serum and SF of RA patients compared with OA patients, and levels of IL-23 were higher in patients displaying an erosive phenotype. Of interest, IL-23 was mostly expressed by synovial fibroblasts upon stimulation by IL-17 [34]. More specifically, RA synovial fibroblasts exhibited a stronger IL-23p19 induction in response to IL-17, and IL-23 secretion is stimulated by TNF and IL-1β, suggesting a pro-inflammatory feedback loop in RA synovium [35, 36]. Macrophages isolated from RA patients' blood similarly showed a higher capacity to produce IL-23 in response to toll-like receptor 2 ligand-mediated agonism [37]. In addition, another study investigating synovial fluid and synovial tissue in RA has shown a higher expression of IL-23 and IL-17F but not IL-17A at both transcriptional and protein levels in patients displaying ectopic lymphoid follicle (ELF) in their synovium compared with those without, suggesting a direct effect of IL-23 in ELF genesis [38]. Notwithstanding the above, it is fair to note

Table 2 Therapeutic agents blocking IL-23–IL-17 axis in PsA

Target	Agent	Structure	Randomized controlled trial	Comparator	Primary outcome	Effect on radiographic progression
Anti-IL-12/23p40	Ustekinumab	Fully human mAb	PSUMMIT1 NCT01009086 Phase III	Placebo	ACR20 week 24: Ust 45 mg 42.4% Ust 90 mg 49.5% Placebo 22.8%	
			PSUMMIT 2 NCT01077362 Phase III	Placebo	ACR20 week 24: Ust 45 mg 43.7% Ust 90 mg 43.8% Placebo 20.2%	Change of mTSS at week 24 compared with baseline (*vs* placebo): Ust 45 mg 0.40 ($P = 0.018$) Ust 90 mg 0.39 ($P \leq 0.001$) Placebo 0.97
Anti-IL-17A	Secukinumab	Human IgG1 mAb	FUTURE1 NCT01392326 Phase III	Placebo	ACR20 week 24: Sec 75 mg 50% Sec 150 mg 50.5% Placebo 17.3%	
			FUTURE2 NCT01752634 Phase III	Placebo	ACR20 at week 24: Sec 75 mg 29.3% Sec 150 mg 51% Sec 300 mg 54% Placebo 15.3%	
			FUTURE3 NCT01989468 Phase III	Placebo	ACR20 at week 24: Sec 150 mg 42% Sec 300 mg 48.2% Placebo 16.1%	
			FUTURE4 NCT02294227 Phase III	Placebo	ACR20 at week 16: Sec 150 mg with load 41.2% Sec 150 mg without load 39.8% Placebo 18.4%	
			FUTURE-5 NCT02404350 Phase III	Placebo	ACR20 at week 16: Sec 150 mg with load: 59.5% Sec 150 mg without load: 55.5% Sec 300 mg without load: 62.6% Placebo 27.4%	Change of mTSS at week 24 compared with baseline (*vs* placebo): Sec 150 mg with load: 0.13 ($P = 0.0061$) Sec 150 mg without load: −0.10 ($P = 0.0048$) Sec 300 mg without load: 0.02 ($P = 0.0003$) Placebo: 0.50
			NCT03623867 Phase III	Placebo	Difference in changes in the volume of erosions on MCP joints 2–4 measured by HR-pQCT at 24 and 48 weeks	

(continued)

Table 2 Continued

Target	Agent	Structure	Randomized controlled trial	Comparator	Primary outcome	Effect on radiographic progression
	Ixekizumab	Humanized IgG4 mAb	SPIRIT-P1 NCT01695239 Phase III	Placebo Adalimumab	ACR20 at week 24: Ixe 80 mg Q2W 54.7% Ixe 80 mg Q4W 62.1% Ada 40 mg Q2W 54.9% Placebo: 30.2%	
			SPIRIT-P2 NCT02349295 Phase III	Placebo	ACR20 at week 24: Ixe 80 mg Q2W 48% Ixe 80 mg Q4W 53.3% Placebo: 19.5%	
			SPIRIT-P3 NCT02584855 Phase III	Placebo	Time to relapse Ixe: NA ($P < 0.001$) Placebo: 22.29 weeks	
	Netakimab (BCD-085)	Humanized mAb	PATERA NCT03598751 Phase III	Placebo	ACR20 at week 24	
	Izokibep (ABY-035)	Fusion protein	NCT04713072 Phase II	Placebo		
Anti-IL-17A and IL-17F	Bimekizumab	Humanized mAb	BE ACTIVE NCT02969525 Phase II	Placebo	ACR50 at week 12 Bkz 16 mg 26.8% Bkz 160 mg 41.5% Bkz 320 mg then 160 mg 46.3% Bkz 320 mg 24.4% Placebo 7.1%	
			BE ACTIVE 2 NCT03347110 Phase II	NA	Safety	
			BE COMPLETE NCT03896581 Phase II	Placebo	ACR50 at week 16	
			BE OPTIMAL NCT03895203 Phase III	Placebo Adalimumab	ACR50 at week 16	
			BE VITAL NCT04009499 Phase III	NA	Safety	
Anti-IL-17RA	Brodalumab	Fully human immunoglobulin G2 mAb	NCT01516957 Phase II	Placebo	ACR20 at week 12 Bro 140 mg 39.6% Bro 280 mg 44% Placebo 19.2%	
			AMVISION1 NCT02029495 Phase III	Placebo	ACR20 at week 16 Bro 140 mg 39.5% Bro 210 mg 51.8% Placebo 16%	
			AMVISION-2 NCT02024646	Placebo	ACR20 at week 16 Bro 140 mg 50.9%	

(continued)

Table 2 Continued

Target	Agent	Structure	Randomized controlled trial	Comparator	Primary outcome	Effect on radiographic progression
			Phase III		Bro 210 mg 44.3% Placebo 24.8%	
Anti-IL-23p19	Guselkumab	Human immunoglobulin G1 lambda (IgG1λ) mAb	Discover-1 NCT03162796 Phase III	Placebo	ACR20 at week 24 Gus100 mg Q8W 52% Gus100 mg Q4W 59.4% Placebo 22.2%	
			Discover-2 NCT03158285 Phase III	Placebo	ACR20 at week 16 Gus100 mg Q8W 64.1% Gus100 mg Q4W 63.7% Placebo 32.9%	Change of mTSS at week 24 compared with baseline (units, compared with placebo): Gus100 mg Q8W 0.52 ($P = 0.071$) Gus100 mg Q4W 0.29 ($P = 0.011$) Placebo 0.95
			COSMOS NCT03796858 Phase III	Placebo	ACR20 at week 24	
	Tildrakizumab	Humanized IgG1/k mAb	INSPIRE 1 NCT04314544 Phase III	Placebo	ACR20 at week 24	Change of mTSS at week 52 compared with baseline
			INSPIRE 2 NCT04314531 Phase III	Placebo	ACR20 at week 24	Change of mTSS at week 52 compared with baseline
			NCT02980692 Phase II	Placebo	ACR20 at week 24	
	Risankizumab	Humanized mAb	KEEPsAKE 1 NCT03675308 Phase III	Placebo	ACR20 at week 24	Change of mTSS at week 24 compared with baseline
			KEEPsAKE 2 NCT03671148 Phase III	Placebo	ACR20 at week 24	
			NCT02719171 Phase II	Placebo	ACR20 at week 16 Riz 75 mg W0 65% Riz 150 mg W0, W12 59% Riz 150 mg W0, W4, W16 61.9% Riz 150 mg Q4W 57.1 Placebo 37.5%	
Anti TNF-α and IL-17A	Remtolumab	Dual-variable domain immunoglobulin	NCT02349451 Phase II	Placebo	ACR20 at week 12 Rem 120 mg 64.8% Rem 240 mg 75.3% Placebo 25%	

All trials in grey are still ongoing or results are not available yet. HR-pQCT: high-resolution peripheral quantitative computed tomography; mAB: monocolonal antibody; mTSS: Van Der Heijde Modified Total Sharp Score; NA: not available; RA: receptor antagonist; Q*x*W: every *x* week.

that consistent detection of IL-23 subcomponents in RA has been challenging.

PsA is more obviously strongly driven by IL-23. Several studies have demonstrated an increased synovial expression of IL-23A transcripts in synovial tissue from patients with PsA compared with patients with traumatic arthropathies. Other downstream cytokine and chemokine transcripts pertaining to the IL-23–IL-17 axis (IL-17A, IL-21) and promoting ELF genesis [(C-X-C motif) chemokine ligand 13 (CXCL13)] were also upregulated [39]. Higher serum and synovial fluid levels of IL-17 and IL-23 were also reported. A recent study of gene expression profiles in paired skin and synovial tissue confirmed these results, showing upregulation of genes related to ELF formation [CXCL13, C-X-C chemokine receptor type 5 (CXCR5)] and IL-23 axis (IL-23A, IL-12B, IL-23R). As opposed to consistent high skin expression in psoriatic skin lesions, IL-23 axis-related transcripts were inconsistently upregulated in synovial tissue. IL-12B and IL-23R transcript expression levels were increased in patients with higher synovitis scores. No association with synovial pathotypes was reported. On the other hand, IL-23p19 and IL-23R positive cells were significantly higher in patients with higher degrees of inflammation and in lympho-myeloid and diffuse-myeloid pathotypes [40]. Increased expression of IL-23, IL-17A and IL-17RA has been reported by others in synovial tissue. In addition, a co-localization with $CD4^+$ T cells, $CD8^+$ T cells and macrophages has been reported [41, 42]. As discussed, above, the local and systemic release of IL-23 by dendritic cells and macrophages promotes Th17 differentiation. The high levels of IL-23 in both psoriatic skin and PsA synovium lead to the recruitment of IL-17/IL-23 producing $CD4^+$ T helper cells within arthritic joints [43]. Locally, IL-23 will promote Th17 cells leading to the expression and release of their signature effector cytokines such as IL-17, IL-21, IL-22, GM-CSF and chemokines receptors and their ligands (CCR6, CCL20). In addition, $IL\text{-}17^+$ and $IL\text{-}22^+$ $CD4^+$ T cells retrieved from peripheral blood more frequently express IL-23R, hereby enhancing joint or skin recruitment [44]. Innate lymphoid cells (ILCs), NK cells and $\gamma\delta$ T cells are also part of the Th17 family and have been reported to infiltrate the skin of PsA patients and release IL-17A or IL-22 [45–47]. Notably, the ILC3 compartment leading to IL-17A production is increased in PsA patients' blood [48].

IL-23R is expressed in several other cells within the joints and enthesis in both RA and PsA such as macrophages, dendritic cells, neutrophils, synovial fibroblasts, OCs and $\gamma\delta$ T cells, $CD4^+$ effector and memory and $CD8^+$ T cells [49, 50]. It is therefore expected that IL-23R polymorphisms may impact effector function in PsA. Of interest, several single nuclear polymorphisms in genes encoding the IL-12/IL-23 axis, such as *IL12B*, *IL23A*, *IL23R* and *STAT3*, have been reported to confer PsA susceptibility [51, 52]. More specifically, multiple *IL23R* polymorphisms have been associated both with risk of developing psoriasis and PsA and with PsA severity [53–57]. However, the alterations of immune function caused by these SNPs are still to be determined. Conversely, other alleles confer protection against PsA, especially through the reduction of STAT3 phosphorylation leading to impaired production of IL-17 [58–60]. Of interest, the *IL23R* R381Q gene variant leads to reduced L-23-mediated Th17 cell effector function without interfering with Th17 differentiation; others such as the SNP c.1142G>A;p.R381Q reduce the circulating Th17 cell pool along with IL-17A and IL-22 serum levels [59, 60]. On the other hand, it has been debated whether *IL23R* polymorphisms could promote RA with no consensus yet reached [47].

On top of its effect in initiating, promoting and maintaining Th17 cells phenotype, IL-23 has been shown to induce a wide range of effects on different effector cells during arthritis. The release of IL-23 by myeloid cells in the lymph nodes will prime T cells, while it will activate innate immune and resident cells within the joints. IL-23 induces the expression of IL-23R, IL-17 and IL-22 on neutrophils, which are known to play an important role in psoriatic skin, while their participation in synovial inflammation is less clear [49].

In addition, Th17 cells are a key T cell subset in the stimulation of osteoclastogenesis, by different mechanisms [61]. First, the release of IL-17 and RANKL promotes OC differentiation [62]. Secondly, when exposed to IL-17, OC lineage cells upregulate RANK, the receptor for RANKL, therefore rending them more susceptible to differentiate into OC [63]. In addition to its direct effects on bone cells, the pro-inflammatory action of IL-17 is also pro-inflammatory, leading to the production of other pro-inflammatory cytokines such as TNF, IL-1 and IL-6 which adds to its effects on bone resorption in arthritis.

However, it has been also suggested that IL-23 can promote osteoclastogenesis in a Th17 independent manner. IL-23 induces the expression of RANKL in synovial fibroblasts, thereby promoting osteoclastogenesis, although this mechanism has been demonstrated in RA but not PsA [64]. Additionally, in human peripheral blood mononuclear cells, IL-23 showed potential to activate DNAX activating protein of 12 kDa and its immunoreceptor tyrosine-based activation motifs thereby upregulating the activation of OC-associated genes (*TRAP*, *CalCR*, *MMP9*) through OC transcription factor NFATc1 [65]. Similarly, by upregulating the expression of the RANKL receptor, RANK, in OC precursors, IL-23 favours OC differentiation and osteoclastogenesis [66]. Conversely, inhibitory effects of IL-23 have also been reported. Most studies reporting similar findings have been studying mouse models of arthritis or IL-23 deficient mice subsequently leading to bone mass loss [67–69]. Overall, although the role of IL-23 on osteoclastogenesis remains controversial, data from clinical trials of ustekinumab (PSUMMIT-1 and -2) and guselkumab in PsA confirmed that the inhibition of IL-23 could also reduce the progression of bone erosions in patients [70, 71]. IL-23 does not affect osteoblasts differentiation or function, since these cells lack IL-23R expression [72].

Data on a potential modulatory effect of IL-23 on chondrocytes and cartilage remain scarce. Most studies have investigated the IL-23–IL-17 axis in OA, showing a correlation between pain and IL-23 serum levels [73]; and IL-23 was increased in synovial tissue-conditioned medium from an OA patient displaying inflammatory histological features [74]. In inflammatory arthritis, to our knowledge, no study has assessed the direct effect of IL-23. So far, the only data available suggest a role for IL-23, along with downstream cytokine such as IL-17 and GM-CSF, in triggering cartilage damage in experimental arthritis [75], but it is not known whether it happens indirectly though triggering other pro-inflammatory cytokine release or both directly and indirectly [76].

Il-23–IL-17 axis blockade in PsA and RA

Based on the aforementioned data, it appeared that targeting IL-23 could be an effective strategy, similar to IL-17 blockade [77]. Several clinical trials have used antibodies targeting IL-17A (ixekizumab and secukinumab), IL17A and F (bimekizumab) [78], IL-17RA (brodalumab), both IL-17A and TNF (bispecific antibodies and ABT-122, a dual-variable-domain immunoglobulin), the p40 subunit of IL-12 and IL-23 (ustekinumab and briakinumab) or the p19 subunit of IL-23 (tildrakizumab [79], risankizumab [80] and guselkumab). These compounds have also been tested in spondyloarthropathies and psoriasis. Ustekinumab has been shown to reduce cutaneous and articular inflammation along with structural damage with a satisfactory safety profile in PSUMMIT 1 and 2 [70, 81, 82]. Additionally, secukinumab showed very similar results in diverse trials leading to the approval of both compounds for PsA treatment [82–84]. Ixekizumab [85, 86], brodalumab [87] and guselkumab [88] have followed the same paths and further drugs targeting the IL-17–IL-23 axis are in development or currently being assessed in trials [77]. These data are summarized in Table 2.

On the other hand, although numerous pre-clinical studies have suggested a role of IL-23–IL-17 axis in RA pathophysiology, clinical trials have failed to show any efficacy of compounds targeting IL-23 and/or IL-17 thus far [89, 90]. That being said, so far compounds have targeted only the p19 subunit of IL-23 in trials in RA; further studies are warranted to evaluate if targeting the p40 subunit, which is common to IL-12, could represent a more effective strategy.

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Data availability statement

The data underlying this article are available in the article.

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