IL-23 orchestrating immune cell activation in arthritis

Aurélie Najm 1 and Iain B. McInnes 1

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

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,
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 IL23R1 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.
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, Il23a–/– 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

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, Il23a–/– 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
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 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<sup>-/-</sup>) 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<sup>-/-</sup>) mice | No arthritis in CIA; arthritis of equal severity in wild-type mice and Il23a<sup>-/-</sup> mice with passive transfer of serum from arthritic K/BxN mice |
| Cornelissen et al. [30] | Mouse AIA model          | IL-23p19-deficient (Il23a<sup>-/-</sup>) 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.
### 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: | Change of mTSS at week 24 compared with baseline (vs placebo): |
|           |              |                 |                             |            | Ust 45 mg 42.4%| Ust 90 mg 49.5%| Ust 90 mg 43.8% | Placebo 22.8% | Placebo 0.40 ($P=0.018$) |
|           |              |                 |                             |            | Placebo 42.4%  | Placebo 22.8% | Placebo 20.2% | Placebo 0.39 ($P<0.001$) |
| 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% | Placebo 0.13 ($P=0.0061$) |
|           |              |                 |                             |            | Sec 150 mg 50% | Sec 300 mg 54% | Placebo 15.3% | Placebo 0.10 ($P=0.0048$) |
|           |              |                 |                             |            | Placebo 15.3%  | Placebo 0.02 ($P=0.0003$) | Placebo 0.50 | |
|           |              |                 |                             |            | Placebo 0.97   | | |
|           |              |                 |                             |            | | | |

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)
| Target                          | Agent          | Structure                  | Randomized controlled trial | Comparator | Primary outcome                                                                 | Effect on radiographic progression |
|--------------------------------|----------------|----------------------------|-----------------------------|------------|----------------------------------------------------------------------------------|-------------------------------------|
|                                | Ixekizumab     | Humanized IgG4 mAb         | SPIRIT-P1 NCT01695239 Phase III | Placebo    | 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    | Ixe: NA (P < 0.001) Time to relapse                                              | 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         | Bimekzumab     | 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% Safety |
|                                |                |                            | BE COMPLETE NCT03896581 Phase II | Placebo    | ACR50 at week 16                                                                 |                                     |
|                                |                |                            | BE OPTIMAL NCT03895203 Phase III | Placebo    | ACR50 at week 16                                                                 |                                     |
|                                |                |                            | BE VITAL NCT04009499 Phase III | NA         | Safety                                                                         |                                     |
| Anti-IL-17RA                    | Brodalumab     | Fully human immunoglobulin Q2 mAb | NCT01518957 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                                                                 |                                     |
|                                |                |                            | AMVISION-2 NCT02024646 Placebo | Placebo    | ACR20 at week 16                                                                 |                                     |

(continued)
| Target Agent | Structure | Randomized controlled trial | Comparator | Primary outcome | Effect on radiographic progression |
|--------------|-----------|-----------------------------|------------|----------------|-----------------------------------|
| Anti-IL-23p19 | Gusekumab | Phase III | Placebo | Bro 210 mg 44.3% | ACR20 at week 24 |
|              | Human immuno-globulin G1 lambda (IgG1κ) mAb | | | Placebo 24.8% | |
|              | Discover-1 | Phase III | Placebo | Gus100 mg Q8W 52% | ACR20 at week 16 |
|              | NCT03162796 | | | Gus100 mg Q4W 59.4% | |
|              | Placebo | | | Placebo 22.2% | |
|              | Discover-2 | Phase III | Placebo | Gus100 mg Q8W 64.1% | Change of mTSS at week 24 compared with baseline (units, compared with placebo): |
|              | NCT03158285 | | | Gus100 mg Q4W 63.7% | Gus100 mg Q8W 0.52 (P = 0.071) |
|              | Placebo | | | Placebo 32.9% | Gus100 mg Q4W 0.29 (P = 0.011) |
|              | COSMOS | NCT03796858 | Placebo | ACR20 at week 24 | Placebo 0.95 |
|              | Phase III | INSPiRE 1 | | |
|              | NCT04314544 | | | |
|              | Phase III | INSPiRE 2 | | |
|              | NCT04314531 | | | |
| Tildrakizumab | Humanized IgG1/k mAb | Phase II | Placebo | ACR20 at week 24 | Change of mTSS at week 52 compared with baseline |
|              | NCT02980692 | | | |
|              | Phase II | KEEPsAKE 1 | | |
|              | NCT03675308 | | | |
|              | Phase III | KEEPsAKE 2 | | |
|              | NCT03671148 | | | |
|              | Phase III | KEEPsAKE 2 | | |
|              | NCT02719171 | | | |
| Risankizumab | Humanized mAb | Placebo | ACR20 at week 24 | Change of mTSS at week 24 compared with baseline |
|              | NCT02349451 | | | |
| Anti TNF-α and IL-17A | Remtolumab | Dual-variable domain immunoglobulin | Placebo | ACR20 at week 12 | |
|              | NCT02349451 | | | Rem 120 mg 64.8% | |
|              | Phase II | | | 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: monoclonal antibody; mTSS: Van Der Heijde Modified Total Sharp Score; NA: not available; RA: receptor antagonist; QxW: 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-17⁺ and IL-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 γδ 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 γδ 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 rendering 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 been 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 (bspecific 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.

**Funding:** This project was funded by the PARTNER Fellowship Program. This paper was published as part of a supplement sponsored by the Janssen Pharmaceutical Companies of Johnson & Johnson.

**Disclosure statement:** I.B.M. has received honoraria or consultancy fees from Abbvie, BMS, Janssen, Novartis, Amgen, Lilly, Astra Zeneca, GSK, Pfizer, Gilead, Sanofi UCB and University of Glasgow has received research funding from B-c-s, Boehringer Ingelheim, Lilly, GSK, Pfizer, Amgen and UCB.

**Data availability statement**

The data underlying this article are available in the article.

**References**

1. Vignali DAA, Kuchroo VK. IL-12 Family cytokines: immunological playmakers. Nat Immunol 2012;13:722–8.
2. Oppmann B, Lesley R, Blom B et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 2000;13:715–25.
3. Pflanz S, Timans JC, Cheung J et al. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4 T cells. Immunity 2002;16:769–90.
4. Collison LW, Workman CJ, Kuo TT et al. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature 2007;450:566–9.
5. Jones LL, Vignali DAA. Molecular interactions within the IL-6/IL-12 cytokine/receptor superfamily. Immunol Res 2011;51:5–14.
6. Thierfelder WE, van Deursen JM, Yamamoto K et al. Requirement for Stat4 in interleukin-12-mediated responses of natural killer and T cells. Nature 1996;382:171–4.
7. Parham C, Chirica M, Timans J et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rβ1 and a novel cytokine receptor subunit, IL-23R. J Immunol 2002;168:699–708.
8. Hunter CA. New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. Nat Rev Immunol 2005;5:521–31.
9. Ivanova DL, Mundhenke TM, Gigley JP. The IL-12- and IL-23-dependent NK cell response is essential for protective immunity against secondary Toxoplasma gondii infection. J Immunol 2019;203:2944–58.
10. Lee JS, Tato CM, Joyce-Shaikh B et al. IL-23-independent IL-17 production regulates intestinal epithelial permeability. Immunity 2015;43:727–38.
11. Wang H, Kjer-Nielsen L, Shi M et al. IL-23 costimulates antigen-specific MAIT cell activation and enables vaccination against bacterial infection. Sci Immunol 2019;4:eaaaw0402.
12. Ramirez-Alejo N, Santos-Argumedo L. Innate defects of the IL-12/IFN-γ axis in susceptibility to infections by Mycobacteria and Salmonella. J Interferon Cytokine Res 2014;34:307–17.
13. Gately MK, Renzetti LM, Magram J et al. The interleukin-12/interleukin-12-receptor system: role in normal and pathologic immune responses. Annu Rev Immunol 1998;16:495–521.
14. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol 2003;3:133–46.
15. Cua DJ, Sherlock J, Chen Y et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature 2003;421:744–8.
16. Boniface K, Blom B, Liu Y-J, de Waal Malefyt R. From interleukin-23 to T-helper 17 cells: human T-helper cell differentiation revisited. Immunol Rev 2008;226:132–46.

17. Lubberts E. Th17 cytokines and arthritis. Semin Immunopathol 2010;32:43–53.

18. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov 2012;11:763–76.

19. Murphy CA, Langrish CL, Chen Y et al. Divergent pro- and antinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med 2003;198:1951–7.

20. Durant L, Watford WT, Ramos HL et al. Diverse targets of the transcription factor STAT3 contribute to T cell pathogenicity and homeostasis. Immunity 2010;32:605–15.

21. Bettelli E, Carrier Y, Gao W et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006;441:235–8.

22. McGechy MJ, Chen Y, Tato CM et al. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat Immunol 2009;10:314–24.

23. Stritesky GL, Yeh N, Kaplan MH. IL-23 promotes maintenance but not commitment to the Th17 lineage. J Immunol 2008;181:9948–55.

24. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 axis: from mechanisms to therapeutic testing. Nat Rev Immunol 2014;14:585–600.

25. Nakao S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. J Immunol 2003;171:6173–7.

26. Cornelissen F, van Hamburg JP, Lubberts E. The IL-23/IL-12 pathway is required for TLR2-mediated IL-23 production in human synovial macrophages: suppression by cilostazol. Biochem Pharmacol 2013;86:1320–7.

27. Yago T, Nanke Y, Kawamoto M et al. IL-23 and Th17 disease in inflammatory arthritis. J Clin Immunol 2017;6:81.

28. Cornelissen F, van Hamburg JP, Lubberts E. The IL-12/ IL-23 axis and its role in Th17 cell development, pathogenesis and plasticity in arthritis. Curr Opin Investig Drugs 2009;10:452–62.

29. Pfeifle R, Rothe T, Ipseiz N et al. Regulation of autoantibody activity by the IL-23–Th17 axis determines the onset of autoimmune disease. Nat Immunol 2017;18:104–13.

30. Cornelissen F, Mus AM, Asmawidjaja PS et al. Interleukin-23 is critical for full-blown expression of a non-autoimmune destructive arthritis and regulates interleukin-17A and RORC+ T cells. Arthritis Res Therapy 2009;11:R194.

31. Flores RR, Carbo L, Kim E et al. Adenoviral gene transfer of a single-chain IL-23 induces psoriatic arthritis-like symptoms in NOD mice. FASEB J 2019;33:9505–15.

32. Sherlock JP, Joyce-Shaikh B, Turner SP et al. IL-23 induces spondyloarthropathy by acting on RORC+ T cells. Nat Med 2012;18:1069–76.

33. Zaky DSE, El-Nahry EMA. Role of interleukin-23 as a biomarker in rheumatoid arthritis patients and its correlation with disease activity. Int Immunopharmacol 2016;31:105–8.

34. Kim H-R, Cho M-L, Kim K-W et al. Up-regulation of IL-23p19 expression in rheumatoid arthritis synovial fibroblasts by IL-17 through PI3-kinase- α– and p38 MAPK-dependent signalling pathways. Rheumatology (Oxford) 2007;46:57–64.

35. Liu F-L, Chen C-H, Chu S-J et al. Interleukin (IL)-23 p19 expression induced by IL-1β in human fibroblast-like synoviocytes with rheumatoid arthritis via active nuclear factor-κB and AP-1 dependent pathway. Rheumatology (Oxford) 2007;46:1266–73.

36. Goldberg M, Nadiv O, Luknar-Gabor N et al. Synergism between tumor necrosis factor alpha and interleukin-17 to induce IL-23 p19 expression in fibroblast-like synoviocytes. Mol Immunol 2009;46:1854–9.

37. Park SY, Lee SW, Lee WS et al. RhOA/ROCK-dependent pathway is required for TLR2-mediated IL-23 production in human synovial macrophages: suppression by cilostazol. Biochem Pharmacol 2013;86:1320–7.

38. Cañete JD, Celis R, Yeremenko N et al. Ectopic lymphoid neogenesis is strongly associated with activation of the IL-23 pathway in rheumatoid synovitis. Arthritis Res Ther 2015;17:173.

39. Dolcino M, Ottria A, Barbieri A et al. Gene expression profiling in peripheral blood cells and synovial membranes of patients with psoriatic arthritis. PLoS One 2015;10:e0128262.

40. Nerviani A, Di Cicco M, Mahto A et al. A pauci-immune synovial pathotype predicts inadequate response to TNFα-blockade in rheumatoid arthritis patients. Front Immunol 2020;11:845.

41. Melis L, Vandooren B, Kruithof E et al. Systemic levels of IL-23 are strongly associated with disease activity in rheumatoid arthritis but not spondyloarthritis. Ann Rheum Dis 2010;69:618–23.

42. van Baarsen LGM, Lebre MC, van der Coelen D et al. Heterogeneous expression pattern of interleukin 17A (IL-17A), IL-17F and their receptors in synovium of rheumatoid arthritis, psoriatic arthritis and osteoarthritis: possible explanation for nonresponse to anti-IL-17 therapy? Arthritis Res Ther 2014;16:426.

43. Fiocco U, Stramare R, Martini V et al. Quantitative imaging by pixel-based contrast-enhanced ultrasound reveals a linear relationship between synovial vascular perfusion and the recruitment of pathogenic IL-17A-F”IL-23−”CD161+CD4+ T helper cells in psoriatic arthritis joints. Clin Rheumatol 2017;36:391–9.

44. Benham H, Norris P, Goodall J et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. Arthritis Res Ther 2013;15:R136.

45. Cai Y, Shen X, Ding G et al. Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. Immunity 2011;35:596–610.
46 Ward NL, Umetsu DT. A new player on the psoriasis block: IL-17A and IL-22-producing innate lymphoid cells. J Invest Dermatol 2014;134:2305–7.

47 Razawy W, van Driel M, Lubberts E. The role of IL-23 receptor signaling in inflammation-mediated erosive autoimmune arthritis and bone remodeling. Eur J Immunol 2018;48:220–9.

48 Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391:2273–84.

49 Nguyen CT, Bloch Y, Składanowska K, Savvides SN, Adamopoulos IE. Pathophysiology and inhibition of IL-23 signaling in psoriatic arthritis: a molecular insight. Clin Immunol 2019;206:15–22.

50 Keijsers RRMC, Joosten I, van Erp PEJ, Koenen HJPM, van de Kerkhof PCM. Cellular sources of IL-17 in psoriasis: a paradigm shift? Exp Dermatol 2014;23:799–803.

51 Alenius G-M, Friberg C, Nilsson S et al. Analysis of 6 genetic loci for disease susceptibility in psoriatic arthritis. J Rheumatol 2004;31:2230–5.

52 Filer C, Ho P, Smith RL et al. Investigation of association of the IL12B and IL23R genes with psoriatic arthritis. Arthritis Rheum 2008;58:3709–9.

53 Bojko A, Ostasz R, Białecka M et al. Association of interleukin 23 receptor variants with psoriasis susceptibility and HLA-C06 genetic variants in psoriasis susceptibility. J Rheumatol 2004;31:2230–5.

54 Keijsers RRMC, Joosten I, van Erp PEJ, Koenen HJPM, van de Kerkhof PCM. Cellular sources of IL-17 in psoriasis: a paradigm shift? Exp Dermatol 2014;23:799–803.

55 Bowes J, Barton A. The genetics of psoriatic arthritis: a paradigm shift? Exp Dermatol 2014;23:799–803.

56 Eirí Írs N, González-Lara L, Santos-Juanes J et al. Genetic variation at IL12B and IL23R is associated with psoriatic arthritis. Int J Immunogenetics 2014;41:335–7.

57 Cargill M, Schrodi SJ, Chang M et al. Association of interleukin 23 receptor variants with psoriatic arthritis. J Rheumatol 2009;36:137–40.

58 Rahman P, Inman RD, Maksymowych WP et al. Association of interleukin 23 receptor variants with psoriatic arthritis. J Rheumatol 2009;36:137–40.

59 Sarin R, Wu X, Abraham C. Inflammatory disease protective R381Q IL23 receptor polymorphism results in decreased primary CD4+ and CD8+ human T-cell functional responses. Proc Natl Acad Sci U S A 2011;108:9560–5.

60 Meglio PD, Cesare AD, Laggnner U et al. The IL23R R381Q gene variant protects against immune-mediated diseases by impairing IL-23-induced Th17 effector response in humans. PLoS One 2011;6:e17160.

61 Gravallese EM, Schett G. Effects of the IL-23-IL-17 pathway on bone in spondyloarthritis. Nat Rev Rheumatol 2018;14:631–40.

62 Sato K, Suematsu A, Okamoto K et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med 2006;203:2673–82.

63 Yago T, Nanke Y, Kawamoto M et al. IL-23 induces human osteoclastogenesis via IL-17 in vitro, and anti-IL-23 antibody attenuates collagen-induced arthritis in rats. Arthritis Res Ther 2007;9:R96.

64 Li X, Kim K-W, Cho M-L et al. IL-23 induces receptor activator of NF-κB ligand expression in fibrobサイト-like synoviocytes via STAT3 and NF-κB signal pathways. Immunol Lett 2010;127:100–7.

65 Shin H-S, Sarin R, Dixit N et al. Crosstalk among interleukin 23 and DNA activating protein 12-dependent pathways promotes osteoclastogenesis. J Immunol 2015;194:316–24.

66 Chen L, Wei X-Q, Evans B, Jiang W, Aeschlimann D. IL-23 promotes osteoclast formation by up-regulation of receptor activator of NF-κB (RANK) expression in myeloid precursor cells. Eur J Immunol 2008;38:2845–54.

67 Adamopoulos IE, Tessmer M, Chao C-G et al. IL-23 is critical for induction of arthritis, osteoclast formation, and maintenance of bone mass. J Immunol 2011;187:951–9.

68 Quinn JM, Sims NA, Saleh H et al. IL-23 inhibits osteoclastogenesis indirectly through lymphocytes and is required for the maintenance of bone mass in mice. The Journal of Immunology 2008;181:5720–9.

69 Kamiya S, Nakamura C, Fukawa T et al. Effects of IL-23 and IL-27 on osteoblasts and osteoclasts: inhibitory effects on osteoclast differentiation. J Bone Miner Metab 2007;25:277–85.

70 Kavanaugh A, Ritchlin C, Raham P et al.; PSUMMIT-1 and 2 Study Groups. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. Ann Rheum Dis 2014;73:1000–6.

71 Deodhar A, Helliwell PS, Boehncke W-H et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1115–25.

72 Zhang J-R, Pang D-D, Tong Q et al. Different modulatory effects of IL-17, IL-22, and IL-23 on osteoblast differentiation. Mediators Inflamm 2017;2017:5950395.

73 Askari A, Naghizadeh MM, Homayounfar R, Shahi A et al. Increased serum levels of IL-17A and IL-23 are associated with decreased vitamin D3 and increased pain in osteoarthritis. PLoS One 2016;11:e0164757.

74 Deligne C, Casulli S, Pigent A et al. Differential expression of interleukin-17 and interleukin-22 in inflamed and non-inflamed synovium from osteoarthritis patients. Osteoarthritis Cartilage 2015;23:1843–52.

75 van Nieuwenhuijze A, Dooley J, Humblet-Baron S et al. Defective germinal center B-cell response and reduced arthritic pathology in microRNA-29a-deficient mice. Cell Mol Life Sci 2017;74:2095–106.
76 Lubberts E. The IL-23-IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol 2015;11:415–29.

77 Sakkas LI, Zafiriou E, Bogdanos DP. Mini review: new treatments in psoriatic arthritis. Focus on the IL-23/17 Axis. Front Pharmacol 2019;10:872. doi: 10.3389/fphar.2019.00872.

78 Ritchlin CT, Kavanaugh A, Merola JF et al. Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. Lancet 2020;395:427–40.

79 Mease P, Chohan S, Garcia Fructuoso F et al. Randomized, double-blind, placebo-controlled, multiple-dose, phase 2b study to demonstrate the safety and efficacy of tildrakizumab, a high-affinity anti-interleukin-23p19 monoclonal antibody, in patients with active psoriatic arthritis. Arthritis Rheumatol 2019;71 (Suppl 10): Abstract 2878.

80 Mease PJ, Kellner H, Morita A et al. OP0307 Efficacy and safety of risankizumab, a selective IL-23p19 inhibitor, in patients with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. Ann Rheum Dis 2018;77:200–1.

81 Ritchlin C, Rahman P, Kavanaugh A et al.; PSUMMIT 2 Study Group. Efficacy and safety of the anti-IL-12/23p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990–9.

82 McInnes IB, Mease PJ, Kirkham B et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137–46.

83 Mease P, van der Heijde D, Landewé R et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018;77:890–7.

84 Mease PJ, McInnes IB, Kirkham B et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329–39.

85 Mease PJ, van der Heijde D, Ritchlin CT et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79–87.

86 Nash P, Kirkham B, Okada M et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317–27.

87 Mease PJ, Genovese MC, Greenwald MW et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med 2014;370:2295–306.

88 Deodhar A, Gottlieb AB, Boehncke W-H et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2018;391:2213–24.

89 Yuan N, Yu G, Liu D, Wang X, Zhao L. An emerging role of interleukin-23 in rheumatoid arthritis. Immunopharmacol Immunotoxicol 2019;41:185–91.

90 Smolen JS, Agarwal SK, Ilivano E et al. A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. Ann Rheum Dis 2017;76:831–9.