The IL-23/IL-17 immune axis as a promising new target in the treatment of spondyloarthritis

Nataliya Yeremenko¹², Jacqueline E. Paramarta², Dominique Baeten¹²

¹Department of Clinical Immunology and Rheumatology and
²Laboratory of Experimental Immunology, Academic Medical Center/
University of Amsterdam, Amsterdam, The Netherlands

Curr Opin Rheumatol. 2014 Jul;26(4):361-70
ABSTRACT

Purpose of review
Various novel therapies for spondyloarthritis (SpA) are currently under development. In this review, we discuss the scientific rational to target the interleukin (IL)-23/IL-17 axis in SpA and give an overview of the proof-of-concept trials with drugs directed towards this axis.

Recent findings
Cumulative evidence from genetics (e.g. the strong genetic association with the IL-23 receptor gene), in-vitro models (e.g. the increased IL-23 production upon HLA-B27 misfolding), human expression studies (e.g. the expansion of IL-17 producing innate cells in SpA) and animal models (e.g. the increased IL-17 production in HLA-B27 transgenic rats) strongly supports the involvement of the IL-23/IL-17 axis in the pathogenesis of SpA. Ustekinumab (a monoclonal antibody directed against the common p40 subunit of IL-23 and IL-12), secukinumab, ixekizumab (both monoclonal antibodies directed against IL-17A), and brodalumab a monoclonal antibody against the IL-17RA receptor) have been recently used in proof-of-concept and randomized trials in the ankylosing spondylitis and/or psoriatic arthritis subforms of SpA, with overall very promising clinical efficacy.

Summary
The first results for novel drugs blocking key cytokines in the IL-23/IL-17 axis are promising in SpA and more novel compounds are upcoming. This will teach us more on the role of the IL-23/IL-17 axis in the pathophysiology of SpA.
INTRODUCTION

Spondyloarthritis (SpA) affects approximately 0.5–1.5% of the Western population and is characterized by inflammation of axial and peripheral joints, and extra-articular manifestations such as skin psoriasis and inflammatory bowel disease (IBD). The disease presentation is heterogeneous and comprises the various phenotypic subtypes ankylosing spondylitis, nonradiographic axial SpA (nr-axSpA), psoriatic arthritis (PsA), IBD-related SpA (IBD-SpA), reactive arthritis (ReA) and undifferentiated peripheral SpA (USpA).1 Although the management of SpA patients has improved enormously since the introduction of tumor necrosis factor (TNF) inhibitors more than 10 years ago,2,3 there is still a high unmet need for novel therapeutic alternatives. Up to 40% of patients do not respond sufficiently to TNF inhibitors, either due to intolerance or inefficacy. Moreover, in patients in whom TNF blockade is effective, remission is not long-lasting since a large majority of patients experience relapse of symptoms after treatment discontinuation.4-6 Finally, even when clinical symptoms and inflammation are completely suppressed, TNF blockade does not appear to halt new bone formation.1

Considering the medical need for other therapeutic agents in SpA, proof-of-concept (PoC) studies have been performed with biological agents directed towards interleukin (IL)-1, IL-6, B cells and costimulatory molecules. However, none of these strategies resulted in significant clinical improvement. More recently, several lines of evidence suggest that the IL-23/IL-17 immune axis may be a promising new target in the treatment of SpA. Our knowledge of this cytokine axis has expanded dramatically over the past decade. The potential importance of the IL-23/IL-17 axis for chronic tissue inflammation was originally described in experimental models of T-cell-driven autoimmune diseases,7 but now starts to be confirmed by PoC studies with drugs targeting this axis in a series of human immune-mediated inflammatory diseases.8 In this review, we give a short overview of the IL-23/IL-17 axis, discuss the lines of evidence linking IL-23/IL-17 with SpA, and summarize the emerging results of clinical trials with compounds targeting IL-23/IL-17 in SpA and related inflammatory diseases.

THE INTERLEUKIN-23/INTERLEUKIN-17 AXIS

Studies using IL-23-deficient mice have indicated a crucial role for this cytokine in the pathogenesis of autoimmune inflammation. In particular, it has been demonstrated that animals lacking functional IL-23 are resistant to experimental autoimmune encephalomyelitis (EAE)7 and collagen-induced arthritis.9 Later, it has been recognized that IL-23 mediates this effect by promoting the development of a novel subset of T cells that produce the signature cytokine IL-17 (Th17).9,10 IL-23 is secreted by activated macrophages and dendritic cells as a heterodimer that comprises a unique p19 subunit and the p40 subunit shared with IL-12 (Fig. 1). IL-23 binds to IL-23R on IL-23R-expressing cells. Engagement of IL-23 with the IL-23R complex, composed of IL-23R and IL-12Rβ1, leads to activation of signal transducer and activator of transcription 3’ (STAT-3), which subsequently up-regulates the expression of retinoic acid receptor-related orphan receptor C (RORC), a Th17-specific transcriptional regulator that is critical for the expression of two members of IL-17 family – IL-17A and IL-17F. IL-17A and IL-17F are by far the best characterized cytokines from the six highly conserved IL-17 family
members (IL-17A–F). IL-17A and IL-17F are both covalent homodimers, but the single subunits can also form IL-17A–IL-17F heterodimers. IL-17A, IL-17F and IL-17A–IL-17F all signal through a heteromeric receptor complex consisting of the IL-17RA and IL-17RC subunits (Fig. 1), mainly expressed on epithelial, endothelial and fibroblast cells resulting in activation of (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, which then leads to the production of pro-inflammatory cytokines, chemokines, adhesion molecules, leukocyte recruitment and activation of endothelium hereby playing an important role in directing development of subsequent immune responses. Remarkably, IL-17A is not only a potent inducer of TNF-α, but also synergizes with this cytokine to promote induction of nearly all its target genes, and in many cases synergy has also been observed with IFN-γ and IL-1β (reviewed in 12).

Recent studies have indicated three new important concepts in Th17/IL-17 biology. Firstly, Th17 cells display a marked functional plasticity. Depending on cytokines or pathogens present in the milieu, Th17 cells can change into interferon (IFN)-γ-producing Th1 cells or IL-4-producing Th2 cells, or even coexpress IL-10 exerting tissue-protective and immunosuppressive effects. Secondly, IL-17A is not only produced by canonical Th17 cells but also by a variety of innate and acquired immune cells, including γδ T cells, myeloid cells and innate lymphoid cells (Fig. 1). This implies that the IL-23/IL-17 axis can still play a pathogenic role in disorders which are not primarily driven by (autoreactive) T cells. And thirdly, the role of Th17 cells depends not only on IL-17A but also on other Th17-derived cytokines such as IL-21 and IL-22, as well as on the specific immunological and tissue context in which they are operating. At mucosal surfaces, for example, IL-17 may have a dual role in promoting tissue inflammation and also protecting from fungal infections. Another good example is IL-22, which drives psoriasis-like dermal inflammation and protects from colitis.

TARGETING THE INTERLEUKIN-23/INTERLEUKIN-17 AXIS IN SPONDYLOARTHRITIS

There are multiple lines of indirect evidence for therapeutic targeting of the IL-23/IL-17 axis in SpA (Table 1). First, the disease shows a strong genetic association with a series of protective polymorphisms in the IL-23 receptor (IL23R) gene, including rs11209026 (Arg381Gln). This IL23R gene variant grants protection from IBD, psoriasis and ankylosing spondylitis through selective impairment of IL-17A production due to decreased STAT-3 phosphorylation. Furthermore, identification of additional risk genes related to IL-17 signaling supported significance of the IL-23/IL-17 axis in the pathogenesis of SpA (Table 1). Second, experimental in-vitro and in-vivo models indicate that (Human Leukocyte Antigen (HLA) B27) heavy chain has a specific propensity to misfold during the assembly in the endoplasmic reticulum, which in specific conditions can lead to an unfolded protein response and increased IL-23 production. HLA-B27 heavy chain can also form aberrant disulfide-linked homodimers on the cell surface, which directly trigger KIR3DL2-positive T cells and natural killer (NK) cells to produce IL-17. Third, analysis of the peripheral blood compartment in humans shows that the number of circulating CD4+ IL-17+ cells (including KIR3DL2-expressing T cells and IL-17-producing γδ T cells) is expanded in
Figure 1. The IL-23/IL-17 pathway. Heterodimeric IL-23 consists of p19 (IL-23A) and p40 (IL-12B) subunits and is secreted by activated macrophages and dendritic cells. IL-23 signals via IL-23R in a STAT3-dependent manner. This leads to typical Th17 effector cytokines production by the lineage expressing specific transcription factor RorC. IL-17A, IL-17F and IL-17A–IL-17F-heterodimer signal through heteromeric receptor complex consisted of IL-17RA and IL-17RC subunits. DC, dendritic cell; IL, interleukin; mϕ, macrophage; RorC, retinoic acid receptor-related orphan nuclear receptor; STAT, signal transducer and activator of transcription.

ankylosing spondylitis. Expression studies in the inflamed target tissues, including axial skeleton, peripheral synovitis and subclinically affected gut tissue, indicate a SpA-specific increase in IL-23 and IL-17-producing innate immune cells (Table 1). Fourth, experimental SpA
Table 1. Rationales for targeting IL-23/IL-17 axis in spondyloarthritis

I. Genetics

IL23R R381Q gene variant grants protection from AS through selective impairment of IL-17A production. Other genes involved in SpA susceptibility:

- IL-12B, which encodes the 40-kd (p40) chain, a component of both IL-12 and IL-23,
- STAT-3, JAK-2 and TYK-2, which encode the major signalling molecules activated by the IL-23R,
- Caspase recruitment domain 9 (CARD-9), which encodes a major signalling intermediate in the pathway whereby fungal products induce IL-23 production from dendritic cells (DCs),
- Prostaglandin E receptor 2 subtype EP2 (PTGER-4), which encodes a prostaglandin receptor that drives IL-23 secretion by DCs.

II. In vitro models

Misfolding of HLA-B27 can generate ER stress that orchestrates the unfolded protein response leading to IL-23 production. There are evidences for UPR activation in cells from humans with spondyloarthritis:

- Gene expression profiling revealed enhanced expression of immunoglobulin heavy chain binding protein (BiP) in SpA PBMCs.
- Increased expression of GRP78 in macrophages isolated from peripheral joints of AS compared with OA patients.
- Ankylosing spondylitis macrophages produce increased levels of IL-23.
- HLA-B27 is capable of forming H chain homodimers ("B27_2") that interact with the killer-cell Ig-like receptor (KIR) KIR3DL2.
- TCR-stimulated peripheral blood KIR3DL2^+CD4^+ T cell lines from SpA patients secrete increased levels of IL-17.

III. Human expression studies

Peripheral blood
- Increase in Th17 cell (SpA, AS).
- Specific increase in killer immunoglobulin receptor (KIR) KIR3DL2^+CD4^+ Th17 cells (AS).
- Increase in IL23R^+γδ T cell (active AS).
- Monocyte-derived macrophages from the peripheral blood of AS patients produce more IL-23 in response to LPS than healthy controls.
- Monocyte-derived DCs from AS patients and healthy controls produced more IL-23 than cells from rheumatoid arthritis (RA) patients.

Target tissues
- CD15^+ neutrophils and MPO^+ myeloid cells are the major cellular sources of IL-17 in the inflamed bone marrow of affected facet joints.
- IL-23 is overexpressed in AS spinal facet joints comparing to osteoarthritis patients and localized in MPO^+CD15 myeloid precursors and to a lesser extent in CD68^+ or CD163^+ macrophages.
- Specifically increased mast cells are the major source of IL-17 in the inflamed synovial joints of psoriatic and non-psoriatic SpA.
- IL-23 is increased in the gut of SpA patients and has been localized to infiltrating monocytes and Paneth cells.

IV. Animal models

Spondyloarthritis in HLA-B27 transgenic rat is associated with CD4^+ Th17 T cell activation.

Experimental ankylosing enthesitis in (BXSB×NZB) F1 mice is associated with an increase in IL-17 production by T cells.

IL-23 overexpression induces a spondyloarthritis-like disease in B10.RIII mice via RORγt^+CD3^+ CD4^+CD8^− T cells that produce IL-17 and IL-22.

AS, ankylosing spondylitis; GRPT78, glucose-regulated protein, 78 kDa; IL-23R, interleukin-23 receptor; JAK-2, Janus kinase 2; LPS, lipopolysaccharides; STAT-3, signal transducer and activator of transcription 3; TYK-2, tyrosine kinase 2.
in HLA-B27 transgenic rats and experimental ankylosing enthesitis in (BXSB × NZB) F1 mice are associated with an expansion of Th17 cells and an increase in IL-17 production. Moreover, IL-23 overexpression induces SpA-like disease in B10.RIII mice via a previously unidentified population of IL-23R+ resident cells expressing RoRγt (RAR-related orphan receptor gamma) that produce IL-17 and IL-22.

Thus, cumulative evidence from genetics, in-vitro models, human expression studies and animal models strongly supports the involvement of the IL-23/IL-17 axis in the pathogenesis of SpA. It is important to note, however, that all this evidence is circumstantial and that the data emerging from these studies should be interpreted carefully. Indeed, genetic risk factors do not always predict pathogenic involvement of a pathway, as exemplified by the genetic association with IL-6R, but the lack of effect of IL-6 blockade in ankylosing spondylitis. Similarly, the UPR (unfolded protein response) induced by HLA-B27 misfolding has been elegantly shown in cell lines and HLA-B27 tg rats, but it remains to be demonstrated that this phenomenon is also occurring in vivo in our patients.

Also, the exact cellular source of IL-23 and IL-17 in the target tissues remains to be fully defined. Interestingly, IL-23 serum levels are not specifically elevated and do not correlate with disease activity and/or treatment response in SpA. And finally, animal models are key to study mechanistic aspects of the pathways of interest, but poorly mimic human diseases. Systemic IL-23 overexpression, for example, does not only lead to SpA-like enthesitis but can also induce a very severe and destructive myeloid-driven polyarthritis in the same mice. These data indicate that preclinical studies should be interpreted carefully, and highlight the crucial importance of PoC studies in human patients.

**CLINICAL TRIALS TARGETING THE INTERLEUKIN-23/INTERLEUKIN-17 AXIS**

Recognition of the importance of the IL-23/IL-17 axis resulted in a rapidly expanding repertoire of compounds targeting this axis. Ustekinumab (a monoclonal antibody directed against the common p40 subunit of IL-23 and IL-12), secukinumab, ixekizumab (both monoclonal antibodies directed against IL-17A), and brodalumab [a monoclonal antibody against the IL-17RA receptor, thereby blocking IL-17A, IL-17F and IL-17E (also known as IL-25)] have all successfully completed preclinical development programs and have subsequently been tested in randomized controlled trials (RCTs) in psoriasis as first-choice target disease (Fig. 2). All compounds showed very significant clinical efficacy in psoriasis, with 75% improvement in Psoriasis Area and Severity Index (PASI75) scores of 65–85% at week 12.

As psoriasis, ankylosing spondylitis and Crohn’s disease are clinically related conditions sharing the same polymorphisms in the IL-23R; these impressive clinical data in psoriasis provided further indirect support for testing these agents in SpA. However, PoC data in Crohn’s disease showed a quite different picture. A phase II trial with ustekinumab did not reach its primary endpoint, but showed a positive trend in TNF inhibitor failers in a post-hoc analysis. A phase III trial specifically designed to address this question showed a significant effect: 34–40% of the ustekinumab groups versus 24% of the placebo group reached the primary endpoint (clinical response at week 6). In contrast with p40 blockade by ustekinumab, however, PoC
Figure 2. The IL-23/IL-17 pathway as a target in the treatment of spondyloarthritis. The pharmacological mechanism of action is depicted schematically for inhibitors of IL-23 and IL-12 synthesis (apilimod), IL-23p40 (ustekinumab, briakinumab), IL-23p19 (tildrakizumab, guselkumab), IL-17A (secukinumab, ixekizumab), IL-22 (fezakinumab) and a blocker of the receptor IL-17RA (brodalumab).

Trials with IL-17 blockers did not show any benefit. A RCT with secukinumab in 60 patients with Crohn’s disease did not reach its primary endpoint and, if anything, showed deterioration in the active treatment arm versus placebo (<0.1% probability that active treatment was better than placebo at the week 6 primary endpoint). A similar trial with brodalumab was terminated by the sponsor after interim analysis (www.clinicaltrials.gov).
With discrepant results in psoriasis versus Crohn’s disease, the clinical efficacy of drugs targeting the IL-23/IL-17 axis was explored in PoC trials in SpA, in particular, in the ankylosing spondylitis and PsA subtypes (summarized in Table 2). Blocking IL-17A with secukinumab was very efficacious in ankylosing spondylitis (Fig. 2). In a PoC phase II trial with 30 patients, the primary endpoint Assessment of SpondyloArthritis International Society 20% improvement criteria (ASAS20) at week 6 was 59% in secukinumab and 24% in placebo. Moreover, not only the clinical signs and symptoms but also the serum biomarkers of inflammation C-reactive protein (CRP) and S100A8 and S100A9, as well as MRI scores for inflammation, decreased upon active treatment. Subsequently, a PoC open-label trial with ustekinumab in 20 ankylosing spondylitis patients showed clear signs of clinical improvement, with an ASAS40 of 65% at week 24, but there was no significant effect on CRP levels in the whole group but only in the clinical responders and the clinical improvement should thus first be confirmed in a RCT before making firm conclusions. Results for ixekizumab and brodalumab in ankylosing spondylitis are not known yet (Fig. 2).

In PsA, the superiority of ustekinumab above placebo has already been shown in several RCTs. The phase II trial with 146 patients showed that 42% of the ustekinumab-treated PsA patients versus 14% of the placebo-treated patients reached the American College of Rheumatology 20% (ACR20) improvement criteria. This was confirmed in two phase III trials (n=615 and n=312), where ACR20 at week 24 was reached in 42–50% of the ustekinumab group versus 20–23% of the placebo group. This response was still maintained at week 50 for the various ACR scores, and also for the PASI75 score and the Health Assessment Questionnaire-Disability Index (HAQ-DI). Moreover, ustekinumab was also efficacious in patients who previously failed on TNF blockers (week 24 ACR20 response: ustekinumab 36% versus placebo 15%). Of the IL-17 blocking agents, only secukinumab was yet tested and reported in a RCT in PsA, with a trend towards clinical efficacy (week 6 ACR20: secukinumab 39% versus placebo 23%) in a phase II PoC trial with 42 patients. The first results with brodalumab in PsA were reported in abstract form, but are not yet published: in a phase II trial with 168 patients, 37–39% of the brodalumab group reached the ACR20 primary endpoint at week 12 compared to 18% of the placebo group. Importantly, these various compounds did not show unexpected safety concerns so far. Results for ixekizumab are still pending.

Taken together, the first PoC trials with drugs blocking key cytokines of the IL-23/IL-17 axis showed promising results in SpA (Table 2). Both larger long-term trials with these compounds and PoC trials with new compounds are currently in progress. The latter include briakinumab (another IL-12/23 inhibitor targeting the common p40 subunit), tildrakizumab and guselkumab (both monoclonal antibodies targeting the p19 subunit of IL-23), apilimod (a small molecule that selectively suppresses synthesis of IL-12 and IL-23) and fezakinumab (a monoclonal antibody directed against compounds targeting IL-23R, Janus kinases (JAKs) and RORγt (RAR-related orphan receptor gamma), are also in preclinical or clinical development.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Study design</th>
<th>SpA subtype</th>
<th>Treatment arms</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies targeting the common p40 subunit of IL-23 and IL-12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Randomized, double blind, placebo-controlled, cross-over, phase II trial</td>
<td>PsA</td>
<td>Placebo (n=70) Ustekinumab (n=76)</td>
<td>ACR20 week 12:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ustekinumab: 42%</td>
</tr>
<tr>
<td>Ustekinumab&lt;sup&gt;61*&lt;/sup&gt;</td>
<td>Randomized, double blind, placebo-controlled, phase III trial</td>
<td>PsA</td>
<td>Placebo (n=206) Ustekinumab 45 mg (n=205) Ustekinumab 90 mg (n=204)</td>
<td>ACR20 week 24:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ustekinumab 45 mg: 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ustekinumab 90 mg: 50%</td>
</tr>
<tr>
<td>Ustekinumab&lt;sup&gt;62*&lt;/sup&gt;</td>
<td>Randomized, double blind, placebo-controlled, phase III trial</td>
<td>PsA</td>
<td>Placebo (n=104) Ustekinumab 45 mg (n=103) Ustekinumab 90 mg (n=105)</td>
<td>ACR20 week 24:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ustekinumab 45 mg: 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ustekinumab 90 mg: 44%</td>
</tr>
<tr>
<td>Ustekinumab&lt;sup&gt;63*&lt;/sup&gt;</td>
<td>Open label single-arm trial</td>
<td>AS</td>
<td>Ustekinumab (n=20)</td>
<td>ASAS40 week 24:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ustekinumab: 65%</td>
</tr>
<tr>
<td>Briakinumab</td>
<td>Not yet tested in SpA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Small molecules suppressing the synthesis of IL-23 and IL-12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apilimod</td>
<td>Not yet tested in SpA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monoclonal antibodies targeting the p19 subunit of IL-23</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tildrakizumab</td>
<td>Not yet tested in SpA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guselkumab</td>
<td>Not yet tested in SpA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monoclonal antibodies targeting IL-17A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secukinumab&lt;sup&gt;64*&lt;/sup&gt;</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>PsA</td>
<td>Placebo (n=14) Secukinumab (n=28)</td>
<td>ACR20 week 6:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secukinumab: 39%</td>
</tr>
<tr>
<td>Secukinumab&lt;sup&gt;65*&lt;/sup&gt;</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>AS</td>
<td>Placebo (n=6) Secukinumab (n=24)</td>
<td>ASAS20 week 6:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secukinumab: 59%</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Randomized, double blind, placebo-controlled trial</td>
<td>PsA</td>
<td>Still recruiting</td>
<td></td>
</tr>
<tr>
<td><strong>Monoclonal antibodies targeting IL-17RA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brodalumab&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>PsA</td>
<td>Placebo (n=55) Brodalumab 140 mg (n=57) Brodalumab 280 mg (n=56)</td>
<td>ACR week 12:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Brodalumab 140 mg: 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Brodalumab 280 mg: 39%</td>
</tr>
<tr>
<td><strong>Monoclonal antibodies targeting IL-22</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fezakinumab</td>
<td>Not yet tested in SpA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACR20 = American College of Rheumatology 20% improvement criteria; ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement criteria; IL-17RA = IL-17-receptor A.
CONCLUSION

The strong albeit circumstantial evidence that the IL-23/IL-17 axis contributes to SpA pathogenesis has now been confirmed by a series of PoC trials with ustekinumab, targeting the p40 subunit of IL-23 and IL-12, and secukinumab, a monoclonal anti-IL17A antibody, in ankylosing spondylitis and PsA. These promising results open new avenues for treatment of patients with SpA, but many fundamental and clinical questions remain to be answered. Obviously, the long-term efficacy and safety of IL-23 and IL-17 blockers need to be demonstrated in large phase III and IV trials.

Three additional questions, however, are of key translational and clinical relevance. Firstly, how does the IL-23/IL-17 axis relate to the TNF axis? Are both pathways synergistic, as suggested by in-vitro data, or are they redundant in vivo? Are patients failing TNF inhibitors responding well to IL-23/IL-17 blockade or, on the contrary, are nonresponders to inhibition of one pathway also nonresponders to blockade of the other axis? Or should we even consider combination treatment with blockade of both axes? Secondly, at what level should the IL-23/IL17 axis be targeted? Is it more effective to target an upstream component of the pathway, such as p19, as this will not only block IL-17A but also other IL-17 family members and IL-22? Or is it safer to target downstream effectors, such as one specific IL-17 isotype or even one specific cell type producing IL-17 in the target tissue of interest? Thirdly and finally, will inhibition of the IL-23/IL-17 axis not only suppress inflammation but also modify disease progression, in particular, with regard to new bone formation? And, if so, what is then the relative contribution of the different cytokines of this axis (e.g. IL-17A, which is known to costimulate osteoclasts, versus IL-22, which promotes stromal repair) to structural damage?

Answering these key questions will require an integrated approach combining the ongoing clinical trials with translational research into the molecular and cellular pathways of disease.

KEY POINTS

- Cumulative evidence from genetics, in-vitro models, human expression studies and animal models strongly supports the involvement of the IL-23/IL-17 axis in the pathogenesis of SpA.
- Clinical trials with ustekinumab (anti-p40) and secukinumab (anti-IL-17A) generally showed good clinical efficacy in ankylosing spondylitis and PsA; proof-of-concept trials with ixekizumab (anti-IL-17A) and brodalumab (anti-IL-17R) are ongoing.
- Targeting the IL-23/IL-17 axis is also effective in psoriasis, but this effect is less clear in Crohn’s disease.
- More compounds targeting the IL-23/IL-17 axis at different levels are in preclinical and/or clinical development.
- Testing these compounds in the various subtypes of SpA is expected to lead to new therapeutic options of patients as well as to new insights in the pathophysiology of the disease.

Acknowledgements Professor Dr Baeten was supported by a VICI grant from The Netherlands Organization for Scientific Research (NWO) and by a grant from the Dutch Arthritis Foundation (Reumafonds).
REFERENCES

The IL-23/IL-17 axis as promising new target.


6. **Zhang L, Li YG, Li YH, et al.** Increased frequencies of Th22 cells as well as Th17 cells in the peripheral blood of patients with ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum 2012; 64:110–120.


9. **This study shows that defective function in HLA-B27-transgenic rat dendritic cells contributes to disease development by skewing CD4+ T cells toward Th17.**


These important clinical trials show good clinical efficacy of targeting of IL-23/IL-17 axis in PsA and ankylosing spondylitis.


These important clinical trials show good clinical efficacy of targeting of IL-23/IL-17 axis in PsA and ankylosing spondylitis.
