IL-17 Inhibition in Axial Spondyloarthritis

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Opinion statement

Axial spondyloarthritis (axSpA) affects 0.5–1.5 % of western population. Although TNF inhibitor (TNFi) medications have dramatically improved the treatment of this disabling disease, there are almost 40 % of patients who do not respond or have intolerance to TNFi. Several genetic, animal model, translational, and clinical studies have confirmed the role of IL-23/IL-17 pathway in the pathogenesis of the axSpA. This axis could be targeted upstream by inhibiting either IL-23 or IL-23 receptor (IL-23R) or downstream by blocking IL-17 or IL-1RA receptor. Ustekinumab, a monoclonal antibody against p40 subunit of IL-12 and IL-23, and secukinumab, a monoclonal antibody against IL-17, have both demonstrated significant beneficial effect in controlling the disease activity, quality of life, and physical function as well as MRI scores in axSpA. Combined IL-17 and TNF- α blockade is a novel option for the patients with axSpA, which needs to be investigated further. We need prospective trials to evaluate the effect of IL-23/IL-17 axis manipulation on the radiographic progression and also on the extra-articular manifestations of axSpA.

Introduction

Axial spondyloarthritis (axSpA) is an immune-mediated chronic inflammatory disease affecting the axial and peripheral skeleton as well as extra-articular organs such as the skin, gut, and eyes. It is estimated

that 0.5–1.5 % of the population in the western hemisphere is affected by axSpA [1]. With better understanding of the underlying immunopathogenesis, newer targeted therapies are being developed to treat this condition.

TNF inhibitors (TNFi) dramatically improve the symptoms and functional capacity and reduce the disease activity in patients with axSpA [2–6]. Studies with different TNFi show ASAS 20 (Assessment of Spondyloarthritis International Society criterion 20) responses to be about 60 % and ASAS 40 responses to be 40 %. Approximately 20 % of patients reach ASAS partial remission. This implies that a significant number of patients either do not respond to, or only partially respond TNFi. Many patients may develop either loss of efficacy or intolerance to these medications over time. It is still unclear if TNFi slow the new bone formation in patients with axSpA; however, recent studies demonstrate favorable results

[7•]. All of these issues underscore the importance of investigating other pathogenic mechanisms of spondyloarthritis.

Non-TNF-directed biologic agents used in the treatment of rheumatoid arthritis such as anakinra, abatacept, rituximab, and tocilizumab have been tried in axSpA with disappointing results [8–12].

Recent years have seen much progress in understanding the IL-23/IL-17 axis and its role in the pathogenesis of many immune-mediated inflammatory diseases such as multiple sclerosis, psoriasis, and inflammatory bowel disease. Growing evidence from genetic, animal, translational, and clinical studies has confirmed the role of IL-23/IL-17 axis in the pathogenesis of axSpA as well. In this review, we will discuss the role of IL-23/IL-17 axis in the pathogenesis of axSpA and describe how this axis can be successfully manipulated for treatment of this condition.

IL-23/IL-17 axis

IL-23

IL-23 is secreted by activated macrophages and dendritic cells as a heterodimer that comprises a unique p19 subunit, and a common p40 subunit shared with IL-12 [13, 14]. IL-23 binds to IL-23 receptor (IL-23R) on IL-23R-expressing cells, particularly T helper 17 (Th17) cells, innate lymphoid cells like $\gamma\delta$ (gamma delta) T cells and invariant natural killer T (iNKT) cells. Engagement of IL-23 with the IL-23R complex composed of IL-23R and IL-12Rb1 leads to activation of these cells through the signal transducer and activator of transcription 3' (STAT3) pathway. In response to the intracellular STAT3 signaling, there is upregulation of retinoic acid receptor-related orphan receptor (ROR)- γ and ROR- α transcription regulators, which are essential for the effector cells to secrete IL-17A and IL-17F. Of note, IL-23R is not present on naïve T cells, so the main role of IL-23 is terminal differentiation and maintenance of Th17 cells rather than development. IL-23 is now recognized to be essential for the proliferation and terminal differentiation of CD4⁺ Th17 cells, maintaining IL-17 production and ultimately driving the pathogenicity of these cells in multiple models of autoimmunity [12, 13, 15, 16•].

Th17 cells and IL-17

Th17 cells are a unique subset of CD4⁺ T cells discovered in 2005, characterized by their ability to secrete IL-17, a potent pro-inflammatory cytokine and also other distinct cytokines such as IL-21 and IL-22 [17••, 18, 19]. In health, Th17 cells play a prominent role in the clearance of pathogens that are not adequately handled by Th1 or Th2 cells. They are also potent inducers of tissue inflammation and have been associated with the pathogenesis of many experimental autoimmune diseases and human inflammatory conditions such as multiple sclerosis, psoriasis, rheumatoid arthritis, and ankylosing spondylitis [20]. TGF- β , IL-6, and IL-21 act as differentiation factors; IL-23 acts as a growth and stabilization factor; and STAT3,

ROR- γ , and ROR- α act as transcription factors for the development of Th17 cells [20]. Th17 cells demonstrate significant plasticity. Depending upon the cytokines or pathogens present in the tissues, Th17 cells can differentiate into interferon (IFN- γ)-producing Th1 cells or IL-4-producing Th2 cells [21].

IL-17 cytokine family members are the signature cytokines secreted by Th17 cells. Since their discovery, Th17 cells and the cytokines they produce have been implicated in nearly all major autoimmune syndromes. Th17 cells secrete IL-17A and IL-17F which are two of the six highly conserved cytokines (IL-17A–F) in the IL-17 cytokine family. The cytokine IL-17A was discovered in 1993 [22]. IL-17A is commonly described as IL-17, as it is the most influential of the IL-17 cytokine family [17••]. IL-17F has 50 % sequence identity with IL-17A [23]. IL-17A and IL-17F are both covalent homodimers, but the single subunits can also form IL-17A–IL-17F heterodimers [23]. 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, mainly expressed on epithelial, endothelial, and fibroblast cells resulting in activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, which then leads to the production of pro-inflammatory cytokines such as IL-6, IL-8, TNF- α , matrix metalloproteinases, and RANKL in a variety of target cells from fibroblasts to epithelial and endothelial cells, macrophages, dendritic cells (DCs), chondrocytes, and osteoblasts thereby playing an important protective role in mucosal immunity to bacteria and fungi, but also promoting inflammation and bone and cartilage destruction when expressed chronically and in inappropriate locations [24••].

IL-17 and TNF- α have synergistic relation with each other, where IL-17 augments the effect of TNF- α in part by enhancing the expression of TNF receptor 2 (TNFR2) [25] and TNF- α enhances the effect of IL-17 on mRNA stability, leading to increased levels of protein expression. Miossec et al. have proposed that IL-17 could be targeted in the subsets of patients with inflammatory diseases who are not responsive (or insufficiently responsive) to TNFi and, also, the combination of TNFi and IL-17 inhibitors could represent a new approach to control the interactions between the two cytokines in inflammatory disorders [51•]. Synergistic interactions also occur between IL-17 and IL-1. Th17 cells also produce other pro-inflammatory cytokines including IL-6, TNF, IL-22, and IL-21 [17••].

Other sources of IL-17

Innate lymphoid cells are the major contributor of IL-17 in humans, rather than Th17 cells [26, 27]. Innate T cells like γ/δ T cells and iNKT cells upon activation by IL-1 and IL-23 can produce IL-17 independent of TCR–MHC complex engagement [26]. Natural killer cells, mast cells, and neutrophils are some other sources of IL-17. Most of these cell types are activated by IL-23, which can be produced by DCs and macrophages exposed to microbial products. This suggests that IL-23/IL-17 axis can influence the disease even in the absence of Th17 cells.

Role of IL-23/IL-17 axis in axSpA

Multiple genetic, animal model, translational, and clinical studies have confirmed the role of the IL-23/IL-17 axis in the pathogenesis of axSpA, mainly in ankylosing spondylitis.

Genetic studies

Several genetic studies point to the involvement of IL-23/IL-17 axis in the pathogenesis of ankylosing spondylitis. IL-23R gene variant rs11209026 (Arg381Gln) offers protection against IBD [28], psoriasis [29], and ankylosing spondylitis [30] through selective impairment of IL-17A production [15] due to decreased STAT3 phosphorylation [31]. Several other genes including CARD9, IL-12B, IL-6R, IL-27, TYK2, and STAT3 have been implicated in ankylosing spondylitis (AS) and also are directly or indirectly associated with IL-23/IL-17 axis [24••].

Studies on animal models

In the rat model overexpression of HLA-B27 (and human β 2-microglobulin) is sufficient to result in activation and accumulation of CD4⁺ Th17 cells in the gut [18] and affected joints [32].

Animal experiments also show that HLA-B27 misfolding leads to endoplasmic reticulum (ER) stress, resulting in unfolded protein response in macrophages and increased release of IL-23 from activated macrophages as well as upregulation of IL-6 and TNF- α expression [32–35].

HLA-B27 molecule has an unusual property of formation of homodimers on the cell surface. Homodimers of HLA-B27 heavy chain have shown to promote survival of innate lymphoid cells, particularly Th17 cells expressing killer cell Ig-like receptor, KIR3DL2, which then secrete increased quantities of IL-17 [36]. Ligation of KIR3DL2 receptors by HLA-B27 molecules enhances the survival of NK and Th17 cells.

Enthesitis is considered to be the primary pathology in patients with various spondyloarthritis [37]. In the pioneering work on IL-23-overexpressing transgenic mice, Sherlock et al. found a unique type of T cells that were IL-23R⁺ ROR- γ t⁺ CD3⁺ CD4[−] CD8[−], and they were present in the entheses, aortic root, and uvea. These cells, upon activation with IL-23, secrete IL-17A, IL-17F, IL-6, and IL-22, which led to axial and peripheral inflammatory arthritis followed by IL-22-dependent osteoproliferation, suggesting the role of IL-22 in the new bone formation in the axSpA [38••].

Human studies

Human studies show elevated serum and synovial fluid IL-17 and also IL-23 levels in patients with AS and PsA, but their association with disease activity and response to TNFi has been inconsistent [39–42].

The number of Th17 and Th22 cells is also elevated in the peripheral blood of patients with AS and, upon ex vivo stimulation of PBMCs, secreted elevated levels of IL-17 [43, 44].

Similar to animal studies, Bowness et al. found increased numbers of innate T cells expressing KIR3DL2 in the peripheral blood and synovial fluid of patients with AS [36]. Also, there is evidence of increased IL-17 expression at the tissue levels by non-lymphoid cells like mast cells in the synovium of peripheral joints [45] and by neutrophils in the facet joints in patients with SpA [46]. IL-23 is overexpressed in the bone marrow of AS patients mainly by the myeloid cells and macrophages as compared to facet joints from osteoarthritis patients [46]. All these

studies point towards the pathogenic role of IL-23/IL-17 axis in the human axial spondyloarthritis.

Clinical trials of medications targeting IL-23/IL-17 axis in axSpA

Ustekinumab

A prospective, open-label, single-arm, “proof-of-concept” trial (NCT01330901) of subcutaneous ustekinumab, a fully human monoclonal antibody against common p40 subunit of IL-12 and IL-23, showed beneficial effect in the axial disease of 20 active AS patients [47●●]. Ustekinumab was administered subcutaneously at a dose of 90 mg at baseline, week 4, and week 16. At 24 weeks, an ASAS 20 response was observed in 75 % of patients, while 30 % of patients reached ASAS partial remission status. There were also significant improvements in other patient-reported outcomes (AS quality of life (ASQoL), EQ-5D) as well as a reduction in the intake of concomitant NSAIDs. There was a significant reduction of active inflammation as scored using the Berlin scoring method (41 % for the sacroiliac joints and 31 % for the spine) at week 24.

Secukinumab

Secukinumab is fully human monoclonal antibody against IL-17A. It has been found to be very effective in axSpA in phase II as well as phase III studies.

A randomized double-blind proof-of-concept multicenter phase 2 study [48●●] (NCT00809159) of IV secukinumab (10 mg/kg, two doses given 3 weeks apart), compared to placebo (PBO), involved 30 patients with moderate-to-severe AS. At week 6, ASAS 20 response was 59 % in secukinumab group ($n=23$) compared to 24 % with placebo ($n=6$). The mean MRI scores decreased from 9.2 (SD 8.87) at baseline to 5.7 (6.20) at week 28 ($p=ns$) in the secukinumab group but remained unchanged in the placebo group at week 28. The clinical response to secukinumab was also significantly associated with genetic polymorphisms in ERAP1 and showed a trend towards the association with polymorphisms in IL-23R.

The results of two phase 3, randomized, placebo-controlled trials with subcutaneous secukinumab, MEASURE 1 and MEASURE 2, were presented at the 2014 annual meeting of the American College of Rheumatology (ACR).

MEASURE 1 study (NCT01358175) was a 52-week randomized placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing of secukinumab [49●●]. Patients with active AS (fulfilling modified New York Criteria and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4), despite current or previous therapy with NSAIDs, DMARDs, and/or TNFi, were randomized into three groups: secukinumab IV loading dose (10 mg/kg) at 0.2 and 4 weeks followed by 75 mg SC (group A, $n=124$) or 150 mg SC (group B, $n=125$) every 4 weeks or PBO (group C, $n=122$). Non-responder PBO patients (pts) were re-randomized to secukinumab 75 or 150 mg at week 16 and all other PBO patients at week 24. Endpoints included ASAS 20 at week 16 (primary), ASAS 40, hsCRP, ASAS 5/6, BASDAI, and ASAS partial remission.

At week 16, secukinumab groups had significantly higher ASAS 20 responses (group A, 59.7 %, and group B, 60.8 %) compared to PBO (group C, 28.7 %, $p<0.01$). ASAS 20 response rates in TNF-naïve pts were 60.0, 66.3, and 32.6 %, and in the TNF-IR pts, these were 58.8, 45.5, and 18.2 %, in groups A, B, and C,

respectively ($p=0.01$ vs. PBO). Secukinumab groups A and B achieved all the pre-specified secondary outcomes, and the responses were sustained through week 52. The onset of action of secukinumab was as rapid as 1 week. Secukinumab was generally well tolerated. The most common adverse events were upper respiratory tract infection and headache.

Patient-reported outcomes were measured every 4 weeks in the MEASURE 1 study using short-form 36 (SF-36), EuroQoL (EQ-5D), ASQoL, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), and Work Productivity and Activity Impairment-General Health (WPAI-GH) [49••]. Secukinumab significantly improved scores on the SF-36 physical and mental component summaries, ASQoL, EQ-5D, and FACIT-Fatigue versus PBO at week 16. The mean changes from baseline at week 16 were greater than the minimum clinically important difference (MCID) for SF-36.

In the second randomized, multicenter, double-blind, PBO-controlled, phase 3 trial (MEASURE 2; NCT01649375), adult patients with active AS (BASDAI >4) despite adequate NSAIDs were randomized to receive weekly SC secukinumab 75 and 150 mg or PBO for 4 weeks followed by dosing every 4 weeks [49••]. They included a total of 219 patients with inadequate response or intolerance to TNFi (38.4 %) as well as TNFi-naïve patients (61.6 %) with mean disease duration of 6.9 years and mean BASDAI of 6.65. While secukinumab 75 mg did not achieve the pre-specified primary or secondary endpoints, secukinumab 150 mg achieved 61.7 % ASAS 20 response compared to 27 % with PBO ($p=0.001$) at week 16. Secukinumab 150 mg also significantly improved hsCRP, ASAS 40, ASAS 5/6, BASDAI, SF-36 PCS, and ASQoL compared with PBO. Secukinumab 150 mg was found to be useful in both TNF-naïve (ASAS 20 response 68.9 vs. 31.1 % in PBO; ASAS 40 response 44.4 vs. 17.8 %) and TNF-IR (ASAS 20 48.1 vs. 20.7 % in PBO; ASAS 40 response 22.2 vs. 0 %) patients. The risk of serious adverse effects is comparable in all the three groups (5.5, 5.6, and 4.1 %).

Conclusion

The substantial evidence from genetic, animal model, and human studies as well as from clinical trials confirms the role of the Th17-dependent and Th17-independent IL-23/IL-17 pathway in the pathogenesis of axSpA. This information provides exciting novel pathogenic targets for the treatment of patients with axSpA who are not responding to, or only partially responding to, the available treatments like NSAIDs and TNFi (see Table 1). Initial proof-of-concept studies of ustekinumab and secukinumab showed significant benefit in the patients with active AS. Both these molecules also showed improvement in

Table 1. Currently available therapeutic targets and biologic agents targeting IL-23/IL-17 pathway

Mechanism of action	Drug
Monoclonal antibody against p40 subunit of IL-12 and IL-23	Ustekinumab
Monoclonal antibody against p19 subunits of IL-23	Tildrakizumab, guselkumab
Monoclonal antibody against IL-17A	Secukinumab, ixekizumab
Monoclonal antibody against IL-17RA	Brodalumab
Monoclonal antibody against IL-22	Fezakinumab
Small molecule suppressing the synthesis of IL-23 and IL-12	Apilimod

the MRI changes of inflammation after the treatment in the proof-of-concept studies.

With the recent phase 3 studies on secukinumab (Measure 1 and Measure 2), it is clearly evident that IL-17A inhibition results in quick and long-lasting improvement in the symptoms and signs of AS as well as significant improvement in physical function and quality of life.

It would be interesting to see if a blockade of IL-17RA receptor with brodalumab gives similar results as IL-17A inhibition in axSpA. Brodalumab has been found very effective in improving PASI scores as well as response rates of psoriatic arthritis [50]. As IL-17A acts synergistically with TNF- α , IL-6, and also IL-1, it may be possible to combine TNFi and IL-17A inhibition simultaneously to achieve better control of the inflammation by targeting both the inflammatory pathways. In fact, Fischer et al. in a recent study demonstrated that bispecific anti-TNF/IL-17 antibodies were more effective in inhibiting the cytokine, chemokine, and matrix enzyme responses from human mesenchymal cells in vitro. This study also showed that dual (both IL-17 and TNF- α) versus single (either IL-17 or TNF- α) inhibition was more effective in inhibiting the development of inflammation and bone and cartilage destruction in arthritic mice [51]. As IL-17A forms heterodimers with IL-17F and these heterodimers have similar action as of IL-17A homodimers, it would be interesting to study the role of IL-17RA inhibition, which will block the action of IL-17A and IL-17F. Targeting IL-23/IL-17 axis upstream at IL-23 inhibition or IL-23 receptor blockade may also be an option in the treatment of axSpA. It would be worthwhile to monitor the biological and imaging parameters of the new bone formation in patients treated with these medications to evaluate their effect on preventing ankylosis and syndesmophyte formation in axSpA.

Compliance with Ethics Guidelines

Conflict of Interest

Abhijeet Danve declares that he has no conflict of interest.

Atul Deodhar reports grants from Amgen, AbbVie, Janssen, Novartis, Pfizer, and UCB and personal fees from Amgen, AbbVie, Janssen, Novartis, Pfizer, and UCB, outside the submitted work, and Dr. Deodhar has received research grants to conduct studies on secukinumab, a drug described in the manuscript. He is also an author on the published studies on secukinumab and has served on the Advisory Boards for Novartis, the company that owns the drug.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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