

Current perspective on the role of the interleukin-23/interleukin-17 axis in inflammation and disease (chronic arthritis and psoriasis)

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Abstract: TH17 is a lymphocyte subset, which is characterized by its polarization to secrete interleukin (IL)-17. IL-23 is the pivotal mediator responsible for TH17 differentiation and the IL-23/IL-17 axis has been strongly implicated in the pathogenesis of several immune mediated diseases, in particular chronic arthritis and skin psoriasis. This review will summarize the basic immunology and the new monoclonal antibodies, which antagonize this pathway allowing a new therapeutic approach.

Keywords: TH17, IL-17, IL-23, psoriasis, psoriatic arthritis, ankylosing spondylitis

A T-cell subset on the stage: TH17

TH17 is a CD3⁺/CD4⁺ T lymphocyte subset, which is characterized by its polarization to secrete interleukin (IL)-17. The inflammatory cytokine IL-17 has been implicated in self-protection versus protozoa, bacteria, and fungi.¹ The first description of IL-17 production by CD4⁺ T was in 1995,² but only in the last decade the concept of a separate CD4⁺ T subset producing IL-17, distinct from TH1 and TH2 subsets, has strongly emerged in the scientific literature.^{3,4} The old dichotomy in T lymphocyte classification pictured a scenario where antigen stimulation of naïve CD4⁺ T cells could determine the emergence either of TH1 lymphocytes secreting interferon- γ (IFN- γ) implicated in the mechanisms of protection to intracellular pathogens (also playing a major role in autoimmunity), or TH2 lymphocytes producing cytokines such as IL-4, IL-5, IL-6, and IL-13, implicated in the immune processes of defense versus extracellular organisms, humoral immunity, and allergy.

The development of the TH1 subset is triggered by various stimuli, in particular by the cytokine IL-12; an early innate immune reaction driven by natural killer cells is also able to activate the T-bet transcription factor through signal transducer and activator of transcription 1, thus enhancing response to IL-12; this is of importance because the therapeutic monoclonal antibody Ustekinumab is directed toward the IL-12p40 subunit that is shared by both IL-12 and IL-23, and therefore it affects both TH1 and TH17 subsets. The pivotal cytokine IL-23, together with other mediators such as IL-1, tumor necrosis factor alpha (TNF- α), and IL-6, is fundamental in directing naïve CD4⁺ T cells toward the TH17 subset. The possible role of transforming growth factor- β in TH17 differentiation in the human immune system is still controversial, while this has been clearly demonstrated in mice models.⁵ In this regard it is relevant that, in naïve T lymphocytes, transforming growth factor- β and IL-6 induce retinoic acid orphan receptors (ROR γ t and ROR α), triggering the upregulation of IL-23 receptor

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(IL-23R) and therefore easing the polarization to TH17.⁶ The dimeric cytokine IL-23 is included in the IL-12 family and is composed of the two subunits IL-12p40 and IL-23p19, while IL-12 is composed of IL-12p35 and IL-12p40 subunits (IL12-p70).⁷ This dimeric molecule structure has to be considered in drug design for the pharmacological and therapeutic consequences. The structural similarities of these two cytokines are also reflected in their receptors, which share a common subunit. The IL-12 receptor is constituted by IL12Rb1 in association with the IL12Rb2 subunit while the IL-23 receptor is composed of the IL12Rb1 and IL-23R subunits. All the data so far available suggest that IL-23 is the pivotal mediator implicated in the differentiation and maturation of the TH17 subset, as well as in the stimuli for IL-17 secretion.⁸

The TH17 subset is modulated by distinct mediators and mechanisms: IFN- γ and IL-4 downregulate IL-17 secretion,^{3,4,9} IL-2 inhibits TH17 cell maturation by downregulating ROR $\gamma\delta$,¹⁰ IL-27 (an antigen-presenting cell-derived cytokine part of the IL-12 family) inhibits IL-17 synthesis by inducing IL-10 secretion from Treg cells.¹¹ In humans, TH17 cells secrete IL-17A and IL-17F but other cells are also capable of producing IL-17, namely neutrophils, natural killer cells, CD8+ lymphocytes, and $\gamma\delta$ T cells, which can produce other IL-17 family cytokines.¹²

In this regard, it is noteworthy that neutrophils accumulate in the upper layer of psoriatic skin, giving rise to the formation of Munro's microabscesses,¹³ and that neutrophils depletion by means of monoclonal antibodies has been shown to reduce epidermal thickening in mice.¹⁴ Furthermore, innate lymphoid cells such as $\gamma\delta$ T cells are elevated in psoriatic skin and constitutively express IL-23,¹⁵ contributing to aberrant keratinocyte differentiation, acanthosis and hyperplasia, hyperkeratosis and parakeratosis. It is also noteworthy that innate lymphoid cells producing IL-17 and IL-22 are expanded in the gut, in the peripheral blood, synovial fluid, and bone marrow of patients with ankylosing spondylitis (AS), supporting the existence of a multiorgan active axis in the spondyloarthritis (SpA) spectrum of diseases.¹⁶

TH17 lymphocytes are also capable of producing other cytokines such as TNF- α , IL-6,¹⁷ and IL-22.¹⁸ In the scenario of psoriasis pathogenesis, it has to be underlined that IL-22 has been shown to stimulate epidermal hyperplasia and dermal inflammation.¹⁹ Many cells have receptors for and are targets of IL-17, among them monocytes and macrophages, osteoblasts, fibroblasts, endothelial and epithelial cells. IL-17 biological action includes the stimuli to the production of the pro-inflammatory cytokines IL-6, TNF- α , IL-1 β , and IL-8, as well as the induction of homing receptors and chemokines

expression, the upregulation of colony stimulating factors and matrix metalloprotease expression.¹²

IL-23 and the TH17 subset in chronic arthritis

For many years rheumatoid arthritis (RA),^{20,12} psoriasis, and psoriatic arthritis (PsA),^{21,22} as well as AS,^{23,24} were considered to be pathological processes driven by the TH1 subset, and IFN- γ and IL-2 were supposed to be the leading mediators in the generation of the inflammatory cascade. In the recent past, emerging data have underlined the role of the TH17 subset and IL-17 in the pathological mechanisms leading to chronic arthritis such as PsA, AS, and RA, as well as inflammatory bowel diseases (IBDs) and skin psoriasis.

Strong evidence links these diseases to the TH17 subset; first of all the data arising from genome-wide association studies and genetic studies. The susceptibility to skin psoriasis and PsA is associated with alleles of the *IL12B* and *IL23R*.^{25,26} Moreover, AS and Crohn's disease, belonging to the spectrum of SpA together with PsA, are also linked to *IL23R* alleles.^{27,28} This common genetic background easily suggests a common inflammatory pathway, which involves the receptor of IL-23. More data support the importance of the IL-23/TH17 axis in these diseases; IL23p19 and p40 (shared by IL-12p70 and IL-23 cytokines) subunits, but not IL-12p35 (present in IL-12 only), have been strongly detected in involved psoriatic skin as compared with non-lesional skin.²⁹ Furthermore, serum levels of IL-12/23 p40 subunit have been detected at significantly higher levels in PsA patients compared with healthy controls.³⁰ We have previously underlined the importance of the IL-23 cytokine and its receptor in TH17 maturation and function; the experimental data summarized support a primary role of the TH17 subset in SpA and skin psoriasis.

Several data also support the possible involvement of the IL-23/TH17 axis even in RA; both IL-17 and IL-23 have been detected in the synovial membrane, in the synovial fluid as well as in peripheral blood serum;³¹ moreover, IL-23 expression has been correlated with the expression of receptor activator of nuclear factor kappa B ligand at the mRNA level.³² IL-17 and TNF- α are able to induce receptor activator of nuclear factor kappa B ligand, which activates osteoclasts that are responsible for erosions at sites of articular inflammation.¹² These data provide support to the concept that the IL-23/IL-17 axis is involved in the mechanisms of bone erosion and joint destruction. As previously outlined, IBDs are part of the SpA spectrum of diseases and therefore it is of importance to note the report of an overexpression of IL-17

in the gut tissue and sera of these patients,³³ as well as the finding of an increased number of TH17 cells in gut biopsies from Crohn's patients.³⁴

The SpA spectrum of disease has been known for a long time to be associated with the HLA antigen B27. Genome-wide association studies have more recently demonstrated the association with IL-23R and the data previously summarized strongly underline the role of the TH17 subset. In 2011, the Oxford group of Bownes et al nicely summarized the evidence which arose from experimental work done in their laboratory, as well as data from the scientific community, and have linked together the HLA-B27 association with KIR receptors and the IL-23/TH17 axis. B27 is a hetero-trimeric molecule that has the tendency to dissociate from the bound peptide and the β 2microglobulin component. This dissociation allows free heavy chains to form β 2microglobulin-free heavy chain homodimers (B27₂), which are able to stimulate the proliferation, survival and IL-17 production of KIR3DL2+CD4+Th-17 cells; it has been also demonstrated that these effects are mediated by the KIR3DL2/B27₂ pair interaction.^{35,36} It is noteworthy that B27₂ responsive IL-17 producing CD4+ T cells were IL-23R positive and were also able to produce TNF- α and/or IFN- γ . Cells of the T lymphocyte lineage, showing an overlapping TH17 and TH1 phenotype (plasticity) can be detected in SpA patients widening the scenario of their possible role in disease as well as in physiologic functions.

New emerging drugs that interfere with the IL-23/IL-17 axis

The possibility that antagonism of this pathway may allow the key approach in the control of disease activity as well as disease damage in chronic arthritis and in other immune-mediated inflammatory diseases has been tested "in vivo" by means of several new biologic drugs, which target the IL-23/IL-17 axis, as summarized in Table 1. This review will focus on the three compounds, which have been more extensively studied at present, Ustekinumab, Secukinumab, and Brodalumab.

Ustekinumab is an IgG human monoclonal antibody that recognizes the p40 subunit of both IL-12 and IL-23 cytokines, therefore influencing the activity of the TH1 and TH17 pathways. Ustekinumab has been assessed in two Phase III trials in psoriasis; in the first study, patients were treated with 45 mg, 90 mg, or placebo at baseline,³⁷ after 4 weeks and then every 12 weeks. They achieved a PASI75 at week 12 of 67.1%, 66.4%, and 3.1%, respectively; results from the second study were comparable.³⁸ Other measures of response

Table 1 Monoclonal antibodies developed for use in human diseases which interfere with the interleukin (IL)-23/IL-17 axis

IL-17 inhibitors
Secukinumab
Ixekizumab
Brodalumab
IL-23 inhibitors
Guselkumab
Tildrakizumab
IL-12 and IL-23 inhibitors
Ustekinumab

included nail disease and quality of life, which also showed clear improvements. No serious side effects were reported in these two trials.

Ustekinumab was also tested in two Phase III trials in PsA. In PSUMMIT 1, patients with an inadequate response to methotrexate were randomized to receive the same dose regimen as in the psoriasis trials;³⁹ the primary end point was ACR20 at week 24 that resulted in 42.4% and 49.5% in the two active drug arms compared with 22.8% in placebo. Other domains of investigation included enthesitis, dactylitis, skin, nail disease, quality of life, and function, where all results were improved. Similar side effects incidence was noted in the three groups, without opportunistic infections or major cardiovascular events. PSUMMIT 2 trial differed in the inclusion criteria of patients that allowed the recruitment of patients previously exposed to TNF- α antagonists, showing similar significant positive response of the patients in the active arms. Furthermore, pooled radiographic data from the two studies showed an inhibition of structural damage.⁴⁰ Promising preliminary results have been also obtained by the administration of Ustekinumab in AS patients, while no formal data are available on the use of Ustekinumab in RA.⁴¹

Secukinumab is an IgG1k human monoclonal antibody that recognizes IL-17A. Two Phase III studies have been performed in psoriasis (ERASURE and FIXTURE). In the first one, patients were randomized to receive subcutaneous Secukinumab at doses of 300 or 150 mg once weekly for 5 weeks and then every 4 weeks compared with placebo.⁴² PASI75 was reached at week 12 by 81.6%, 71.6%, and 4.5% of patients, respectively. In the FIXTURE study (which compared Secukinumab versus Etanercept) PASI75 was reached by 77.1%, 67.0%, 44.0%, and 4.9% of patients on 300 mg or 150 mg of Secukinumab, 50 mg twice weekly of Etanercept or placebo, respectively. Secukinumab also demonstrated to be effective in nail disease, itch, and quality of life; serious side effects were infrequent and comparable among all arms. Candida infections were reported as mild-moderate in 4.7%,

2.3%, and 1.2% of patients in the 300 mg or 150 mg Secukinumab or Etanercept groups, respectively.

In PsA, Secukinumab has been studied in two Phase III trials (FUTURE 1 and 2 trials). In FUTURE 1, patients were randomized to receive an intravenous loading dose of Secukinumab 10 mg/kg at baseline,⁴³ weeks 2 and 4 and then 150 mg or 75 mg every 4 weeks starting from week 8 compared with placebo. At week 24, ACR20 was 50.0%, 50.5%, and 17.3%, Secukinumab 150 mg, 75 mg, or placebo, respectively. Other domains investigated included skin disease, dactylitis, enthesitis, function, quality of life, and inhibition of X-ray progression of damage, which all resulted statistically different from placebo. In the FUTURE 2 trial, patients did not receive an intravenous loading dose;⁴⁴ results confirmed the efficacy in the same domains as in FUTURE 1 trial. Overall adverse effects in PsA patients were similar to psoriatic patients; the total infection rate was slightly higher in the Secukinumab arm compared with placebo, without opportunistic or tuberculosis infections.

Two Phase III trials have been also performed in AS: MEASURE 1 and MEASURE 2. In the first trial, patients were randomized in three arms after a 10 mg/kg weekly loading dose of Secukinumab for the first 4 weeks, followed by 75 mg or 150 mg or placebo subcutaneously every 4 weeks.⁴⁵ The primary end point was ASAS20 response at week 16, which was reached by 59.7% and 60.8% of patients in the active arms and 28.7% in the placebo group, respectively. In the MEASURE 2 trial, patients did not receive the loading dose;⁴⁶ the ASAS20 responses were 41.1%, 61.1%, and 28.4%, respectively. Side effects were in line with the previous studies.

It is remarkable that a Phase II study performed in RA was not able to separate the active drug arms compared with placebo in terms of ACR20 response,³⁷ although Secukinumab-treated patients showed statistically lower DAS28 scores and lower high sensitivity C-reactive protein values.

Brodalumab is a human monoclonal antibody that blocks IL17A receptor, therefore inhibiting IL-17 signaling. Brodalumab has been proved to be effective in a Phase II study in psoriasis;⁴⁷ patients were treated with 70, 140, 210, or 280 mg of Brodalumab subcutaneously and PASI75 response rates at 12 weeks were 45%, 85%, 86.3%, and 76%, respectively, compared with 16% of placebo controls. A Phase II study was also performed in PsA, aiming to an ACR20 response primary end point at 12 weeks; 37% and 39% of patients treated in the 140 and 280 mg active drug arms reached the primary end point compared with 18% in the placebo arm.⁴⁸ Brodalumab has been studied also in RA,

without benefit. In a Phase I ascending dose study, separation of active drug-treated patients compared with placebo was not demonstrated;⁴⁹ furthermore in a Phase II study performed in methotrexate inadequate responders similar negative results were obtained.⁵⁰

In this study, Pavelka et al reported a clear lack of therapeutic effect of IL-17 antagonism in RA, and the authors' conclusion was that there is no reason to pursue further evaluation of Brodalumab in this disease. Although this is a negative study the lesson that arises from this publication is of value. Together with previously published data for Secukinumab, an anti-IL-17A antibody, the results of this trial strongly indicate that the IL-17 pathway is not an appropriate therapeutic target for RA while it is successful in PsA. This evidence is instructive and may help in clarifying the important pathogenic differences that characterize RA compared with PsA; similar disease in some features, so different in others.

Marketed or developing drugs that inhibit IL-17, IL-23, or the IL-12/IL-23 shared subunit IL-12p40 have demonstrated significant benefit in SpA and skin psoriasis. Further studies and post-marketing data will reveal the best approach in order to efficiently interfere in the pathogenetic mechanisms of TH17-mediated diseases.

Conclusion

The precise pathogenesis of chronic arthritis, skin psoriasis, and IBD, as well as the role of the TH17 subset in their inflammatory milieu, needs further in depth research. Experimental clinical work performed so far in patients with these diseases, thanks to the availability of new biologic compounds targeting the IL-23/IL-17 axis, suggests the important features that differentiate SpA and psoriasis from IBD and RA. These differences are reflected in the response to treatment and therefore deserve our greatest attention.

The availability of new effective drugs that target different mediators and inflammatory pathways is of great importance in order to increase opportunities for the physician to impact in disease activity and progression for the benefit of the patients.

Disclosure

The authors report no conflicts of interest in this work.

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