Blocking Interleukin-12 and Interleukin-23 in the Treatment of Axial Spondyloarthritis

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Opinion statement

Currently, there are only two effective drug classes approved for treatment of ankylosing spondylitis (AS)/axial spondyloarthritis (axSpA): non-steroidal anti-inflammatory drugs (NSAIDs) and, if NSAIDs fail, tumour necrosis factor (TNF)- α blockers. Although the majority of patients do respond well to these treatment options, there is certainly an unmet need for further therapeutic options for patients who do not respond to, do not tolerate or have contraindications for NSAIDs and TNF- α blockers. Blockade of the Th17 pathway that includes inhibition of interleukins (IL)-12/23 and to a further extent IL-17 represent currently the most promising therapeutic targets in axSpA. The first positive results on the blockade of IL-12/23 in active AS should be confirmed in larger placebo-controlled studies, ideally including the entire population of axSpA. It is very important to identify whether IL-12/23 and IL-17 blockade also works in TNF- α blocker non-responders and if there are specific predictors of response to one or another drug class. Also, effects of this therapy on long-term outcomes including progression of structural damage in the spine in AS/axSpA are of high importance and should be evaluated.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease characterized by predominant involvement of the spine and/or sacroiliac joints. Two forms or stages of axial SpA are covered by the

Assessment of Spondyloarthritis International Society (ASAS) classification criteria [1]: a non-radiographic form (no definite structural damage on X-rays of sacroiliac joints and spine), also called non-radiographic

axSpA (nr-axSpA), and a radiographic form (with structural damage on conventional X-rays—radiographic sacroiliitis [2] and/or syndesmophytes in the spine), better known as ankylosing spondylitis (AS) [3].

In contrast to other inflammatory rheumatic diseases, such as rheumatoid arthritis, the therapeutic options in axSpA are limited and include non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line therapy and, if this treatment fails, tumour necrosis factor (TNF)- α blockers. There are some differences in the current approval status for TNF blockers in nr-axSpA and AS. First, in contrast to the EU, none of TNF blockers is approved for nr-axSpA in the USA. Second, not all TNF blockers approved for AS treatment in the EU (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and infliximab biosimilars) are also approved for nr-axSpA (currently available are adalimumab, certolizumab pegol and etanercept; golimumab will probably receive an approval in 2015, infliximab and its biosimilars will probably not be approved for nr-axSpA at all). And third, in AS, TNF-blockers are indicated if high disease activity (as indicated by the Bath Ankylosing Spondylitis Disease Activity

Index—BASDAI value of 4 and higher on a 0 to 10 scale) is present despite NSAIDs therapy (or without NSAIDs if contraindicated/not tolerated). In nr-axSpA, objective signs of inflammation (elevated C-reactive protein—CRP or osteitis on magnetic resonance imaging—MRI) are required in addition to clinical disease activity and failure of NSAIDs for initiation of TNF blocking therapy.

Although NSAIDs and TNF blockers are effective in the majority of axSpA patients, there is still a substantial proportion of patients (20–30 %) who do not respond adequately to the currently available treatment [4–6]. According to the actual version of the joined ASAS/European League Against Rheumatism (EULAR) recommendations, disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids play only a limited role in the treatment of AS and to a further extent of axSpA [7]. Furthermore, the majority of other biologics approved for or effective in the treatment of rheumatoid arthritis (targeting T cells—abatacept, B cells—rituximab, IL-1—anakinra or IL-6—tocilizumab and sarilumab) failed to demonstrate clinical efficacy in AS [8–11]. Thus, there is still an unmet need for new therapeutic options in axSpA.

The role of Th17 axis, IL-12 and IL-23 in axial spondyloarthritis

Th17 cells is a recently identified T cell subset deriving from naive T cells under influence of IL-23 [12]. IL-23 together with TGF- β and IL-6 stimulates naive precursors cells to differentiate into a Th17 subset producing proinflammatory cytokines (IL-17A, IL-17F, IL-6 and TNF- α) [12–14]. Even more important seems to be the role of IL-23 in maintaining the Th17 phenotype and to acquire the full effector function [15, 16]. Currently available data indicate that Th17 cells play a crucial role in the number of chronic autoimmune diseases including psoriasis, psoriatic arthritis and other spondyloarthritides such as AS/axSpA [17–19].

In AS, an increased number of circulating polyfunctional Th17 cells and an elevated level of serum IL-17 were reported [20–23]. Furthermore, an immunohistological analysis of IL-17 secreting cells in facet joints from AS patients indicates a significantly higher frequency of IL-17-producing cells compared to facet joint samples obtained from patients non-inflammatory spinal disorders [24]. Clinical efficacy of IL-17 blockade with a fully human antibody to IL-17A (secukinumab, formerly AIN457, Novartis) was demonstrated in two phase III trials in psoriasis [25] and in proof-of-concept trials in psoriatic arthritis [26] and AS [27•]. Most recently, positive results of the phase III programme with secukinumab in PsA [28] and AS [29, 30] were presented. It could be expected that secukinumab will be consequently approved for the treatment of psoriasis, psoriatic arthritis and AS in 2015–2016.

Secukinumab will be probably followed by two further IL-17 inhibitors: ixekizumab (Lilly) [31]—a humanized anti-interleukin-17 monoclonal antibody and brodalumab (Amgen) [32]—human anti-interleukin-17-receptor monoclonal antibody, which are currently at different stages of the clinical study programme in psoriasis, psoriasis arthritis and AS/axial SpA.

There is an increasing evidence that IL-23 plays a central role in several autoimmune diseases including SpA. IL-23 is a heterodimeric cytokine sharing the 40-kDa heavy chain (p40) with IL-12. The light chains are different in these two cytokines: p35 in IL-12 and p19 in IL-23 [33]. Despite structural similarity, IL-12 and IL-23 have discrete roles in the regulation of T cell immunity. IL-12 is an important factor for the differentiation of naïve T cells into IFN- γ -producing Th1 cells. Using IL-12 p40-deficient mice and anti-p40 antibodies, it was demonstrated that p40 was required for the development of T-cell-mediated autoimmune diseases such as experimental allergic encephalomyelitis (EAE), collagen-induced arthritis (CIA), and inflammatory bowel disease [16]. However, IFN- γ -deficient mice remained susceptible to these diseases, suggesting that IFN- γ is not essential for the modelled autoimmune disorders [16]. Further studies showed that mice deficient in either the p19 subunit (lacking IL-23 alone) or the p40 subunit (lacking both IL-12 and IL-23) were resistant to EAE and CIA, whereas p35-deficient mice (lacking IL-12 only) remained susceptible to these diseases [34]. These data indicated that rather IL-23 and not IL-12 is essential for the development of at least some of the autoimmune disease.

A genome-wide association studies showed that polymorphism in IL-23 receptor is associated with susceptibility to AS [35, 36]. Misfolding of HLA-B27 in carriers of this antigen might lead to induction of unfolded protein response in the macrophages with an increased IL-23 production by these cells [37, 38] that its turn leads to activation of Th17 cells. It was also demonstrated that IL-23 is able to induce SpA-specific enthesal inflammation *in vivo* [39]. Finally, *in situ* analysis of IL-23-positive cells in bone marrow and in fibrous tissue replacing bone marrow in facet joints of AS patients revealed a significantly higher number of IL-23-producing cells in comparison to samples obtained from patients without inflammatory spinal disorder [40], and elevated IL-23 levels were found in peripheral blood and synovial fluid in AS patients [23, 41]. In the following part, we will discuss the therapeutic potential of IL-12 and especially IL-23 blockade in axSpA.

Blockade of IL-12 and IL-23 in axial spondyloarthritis

Currently, there is only one approved drug blocking IL-12 and IL-23—ustekinumab (STELARA, Centocor/Johnson & Johnson/Janssen-Cilag). Ustekinumab is a fully human IgG1 κ monoclonal antibody binding with high affinity and specificity to the p40 protein subunits of IL-12 and IL-23. This prevents IL-12 and IL-23 from binding to their IL-12R β 1 receptor protein expressed on the surface of immune cells. Ustekinumab has been shown to be effective in the treatment of psoriasis [42–44] and psoriatic arthritis [45, 46, 47] that resulted in the approval of ustekinumab in the EU and in the USA for treatment of these two conditions. The approved dose of ustekinumab is 45 mg (90 mg for patients with body weight >100 kg) administered

subcutaneously at weeks 0 and 4 and every 12 weeks thereafter. There is also a signal that ustekinumab might be effective in Crohn's disease [48]. Less data are available concerning efficacy of ustekinumab in axSpA.

In a phase III trial with ustekinumab in psoriatic arthritis (PSUMMIT 1), 172 of 615 patients had axial involvement (spondylitis). In this subgroup, treatment with ustekinumab resulted in a ≥ 50 % improvement of the BASDAI (BASDAI50 response) at week 24 in 23.5 % (12/51) of the patients who received ustekinumab 45 mg, 31.7 % (19/60) of the patients treated with ustekinumab 90 mg as compared to 13.1 % (8/61) in the placebo-treated group (statistically significant was only the difference ustekinumab 90 mg vs. placebo, $p=0.014$) [46•].

We performed recently a proof-of-concept open-label trial with ustekinumab in patients with active AS (TOPAS) [49•]. In this trial, ustekinumab in a dose of 90 mg was administered subcutaneously at baseline, week 4 and week 16 in 20 patients with active AS. Active disease was defined as a BASDAI score of ≥ 4 despite NSAIDs treatment. At week 24, Assessment of SpondyloArthritis International Society (ASAS)40 response (the primary end-point) was reached by 65 % of the patients. ASAS20 response, BASDAI50 response and ASAS partial remission were achieved by 75, 55 and 30 % of the patients, respectively. In line with these data, 50 and 20 % of the patients achieved the AS disease activity score (ASDAS) clinically important improvement and major improvement, respectively. At week 24, 35 % of the patients had an ASDAS inactive disease (ASDAS <1.3). Importantly, there was a correlation between clinical response and improvement of objective markers of inflammation—serum CRP and osteitis in the axial skeleton on MRI. CRP serum level at week 24 went down as compared to baseline in the ASAS40 responders group (-1.1 ± 7.5 mg/l) while there was even a CRP increase in non-responders ($+3.3 \pm 3.5$ mg/l), $p=0.008$. Similarly, osteitis change score in the sacroiliac joints at week 24 was -3.1 ± 3.8 in ASAS40 responders as compared with $+0.6 \pm 1.3$ in non-responders, $p=0.015$; osteitis change score in the spine after 24 weeks of treatment was -1.9 ± 1.9 in ASAS40 responders as compared with $+1.0 \pm 2.4$ in non-responders, $p=0.023$ [49•]. Thus this small proof-of-concept study provided a signal that ustekinumab (and in general blockade of IL-12/23) might be effective for treatment of active AS/axial SpA. These results should be confirmed in a larger placebo-controlled trial, ideally including the entire spectrum of axSpA: AS and nr-axSpA. A further step would be to demonstrate efficacy of ustekinumab in patients not responding to TNF blockers and to identify specific predictors of response to one or another drug class if any. And finally, an effect of IL-12/23 blockade on structural damage progression in the spine in axSpA should be investigated.

Another anti-p40 monoclonal antibody briakinumab (Abbott/AbbVie) has been successfully studied in psoriasis [50, 51], but further development of the drug was suspended.

There are several anti-p19 antibodies blocking, therefore, IL-23 only, which are at different stages of the clinical development programmes. The BI 655066 compound (Boehringer Ingelheim)—a monoclonal antibody against p19 subunit of IL-23—is being currently investigated in psoriasis (studies with clinicaltrials.gov identifiers NCT02203851 and NCT02054481), Crohn's disease (NCT02031276) and AS (NCT02047110). Guselkumab (Janssen)—also an anti-IL-23 p19 antibody—has entered an extensive study programme in

psoriasis [52] and is also under investigation in psoriatic arthritis now (NCT02319759). The third anti-IL 23p19 antibody, which is underway in a clinical trial in psoriasis now, is tildrakizumab (Merck Sharp & Dohme, study NCT01722331). It could be expected that these drugs will also consequently be tested in other forms of SpAs and SpA-related conditions in the next years.

So far, no new safety issues (as compared to TNF-blockers) has been raised in relation to IL-12/23 inhibition (with data mainly related to ustekinumab [53, 54]); standard precautions concerning infection risk including tuberculosis should be applied upon initiation of anti-IL-12/23 therapy.

Conclusion

IL-12/23 and IL-17 represent nowadays the most promising future therapeutic targets in axial SpA/AS. It seems that efficacy of IL-12/23 or IL-17 blockade on the entire group level is similar to that in TNF blockers. Therefore, it is extremely important to find out if there are patients responding to one drug class and not responding to another one—trials in patients with AS/axial SpA who failed to respond to anti-TNF therapy and studies with cross-sectional design and head-to-head comparisons of biologics should follow. In addition, long-term data with analysis of the impact of the novel drugs on radiographic spinal progression are of high interest and clinical relevance.

Compliance with Ethics Guidelines

Conflict of Interest

Denis Poddubnyy reports grants from Janssen-Cilag, during the conduct of the study; personal fees from AbbVie, MSD, Novartis, Pfizer, and UCB; personal fees from AbbVie, Bristol-Myers Squibb, Janssen-Cilag, MSD, Novartis, Pfizer, Roche, and UCB, outside the submitted work.

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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