IL-17 INHIBITION: EMERGING PERSPECTIVES IN THE FUTURE MANAGEMENT OF AXIAL SPONDYLOARTHRITIS

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MEETING SUMMARY

The meeting was opened by Prof Atul Deodhar who introduced the prevalence, epidemiology, and clinical features of axial spondyloarthritis (axSpA), and discussed the ongoing unmet needs in the management of axSpA. Prof Dirk Elewaut described the role of the interleukin-17 (IL-17) pathway in the pathogenesis of axSpA. Prof Dominique Baeten reviewed the latest clinical data from existing and emerging therapies for axSpA. Finally, Prof Xenofon Baraliakos discussed recent advances in the assessment of bone inflammation and structural damage in axSpA. Each discussion was followed by questions and answers. The meeting was concluded with an interactive final discussion between the panellists and the audience, with concluding remarks by Prof Atul Deodhar.

Welcome and Introduction

Professor Atul Deodhar

Low back pain is a highly prevalent condition. In the USA alone, chronic low back pain, defined as a low back pain that persists for >3 months, has been estimated to affect up to 20% of the population at any given time.[1,2] Mechanical back pain accounts for most cases, although back pain can also be inflammatory in nature or due

to other pathologies such as fractures, infection, or tumours.[2] Approximately 15% of patients with long-term inflammatory back pain can develop axSpA, a condition which mainly causes painful inflammation and stiffening of the spine and sacroiliac joints. Patients with inflammatory back pain initially develop non-radiographic axSpA (nr-axSpA), which can (in 10% of cases) progress to ankylosing spondylitis (AS) in which radiographic structural damage is observed over a 2-year period. Although axSpA can remit spontaneously in some patients, it leads to significant disability in others.[2]

In a cross-sectional survey conducted in adults (age range: 20-69 years) as part of the 2009 US National Health and Nutrition Examination Survey (NHANES), 0.55% of the participants reported having received a diagnosis of AS. Based on the European Spondyloarthropathy Study Group (ESSG) criteria, 1.4% of the overall population had axSpA.[3] According to some studies, axSpA may be more common than rheumatoid arthritis (RA),[4-7] and, compared with psoriatic arthritis (PsA) or RA, axSpA has also been shown to be associated with the highest decrease in physical health-related quality of life.[8] In a cross-sectional survey conducted in the USA, patients with AS were more likely, compared with the general population, to be work disabled (13.3% versus 5.7%; p<0.0001) or not to work at all (25.1% versus 21.8%; p=0.07).[9] These associations were stronger among patients with chronic AS (≥20 years) and aged ≥45 years. AS patients were also more likely to have never been married (22.8% versus 15.4%; p<0.0001) or divorced (13.2% versus 10.0%; p=0.02) compared with the general population.

As recommended in the treatment guidelines recently developed by the American College of Rheumatology (ACR) in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN), non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy are the first-line treatment options for patients with axSpA (Ward M et al. Arthritis Rheum in press). Anti-tumour necrosis factor (TNF) α therapy should be given to patients with persistently high disease activity despite conventional treatments.[10] Switching from one TNF inhibitor to another can be recommended in patients with loss of response. However, it should be noted that this recommendation is based on observational data and prospective studies, highlighting the need for further randomised controlled studies to support these recommendations.

Across different studies, approximately 60% of patients with AS treated with anti-TNF therapies (e.g. etanercept, adalimumab, infliximab, golimumab, or certolizumab pegol) achieve the 20% response according to the Assessment in Ankylosing Spondylitis International Society criteria for improvement (ASAS20).[11-15] These observations highlight one of the unmet needs in the treatment of AS, in which up to 40% of patients do not achieve acceptable clinical improvement in their condition. The fact that inhibition of bone proliferation is not maintained (as shown by studies of 2 years' duration), and that the presence of opportunistic infections and other complications may be unacceptable to patients, are among additional limitations associated with the use of anti-TNF therapy. It is therefore important that new therapies are developed for the treatment of axSpA.

IL-17 has a central role in the pathogenesis of SpA.[16-18] IL-17 production is induced during both the innate and adaptive immune responses by a range of different cells, acting on many additional cells and tissues to drive production of further pro-inflammatory cytokines and chemokines, which act in a feedback loop to increase IL-17 production. IL-17 is involved in several pathogenic processes such as inflammation and bone erosion, both of which have been implicated in the development of SpA. In this symposium, the rationale for IL-17 inhibition in axSpA was explored together with the latest advances in treatments for axSpA and the effects of current and emerging treatments on inflammation and structural damage.

Why Target IL-17 in Axial Spondyloarthritis?

Professor Dirk Elewaut

The differentiation of naïve T cells into a variety of T helper (T_H) cells, each with different functions, plays an important role in the adaptive immune system. For instance, T_H1 cells function in cell-mediated immunity against intracellular bacteria and viruses, and are characterised by interferon gamma production, whereas T_H2 cells function in humoural immunity against extracellular parasites, and produce cytokines such as IL-4, IL-5, IL-13, and IL-25, while immunoregulation (peripheral

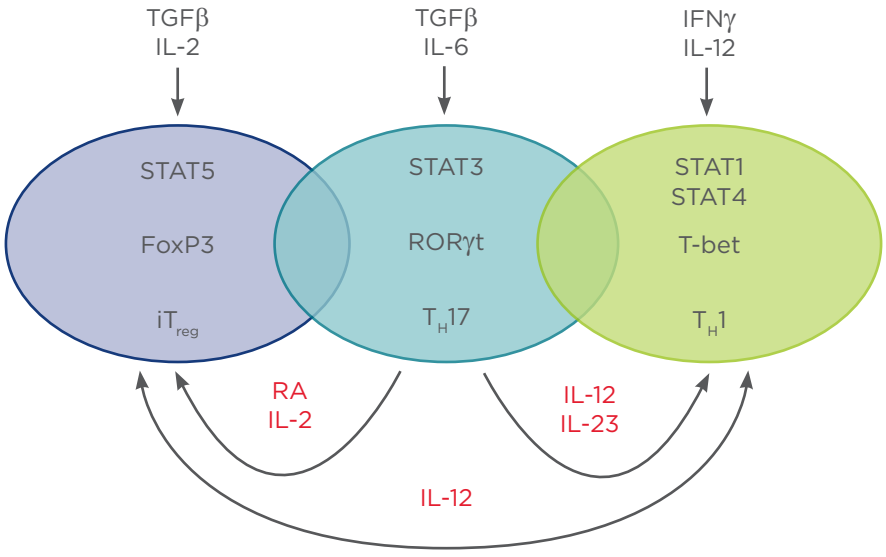
immune tolerance) is mediated by iT_{reg} cells.[19] T_H17 cells also function in cell-mediated immunity but, in contrast to T_H1 cells, they protect against extracellular bacteria and fungi and are characterised by the production of IL-17, as well as IL-22 and IL-26.[19]

Our understanding of the role of IL-23/IL-17 signalling and T_H17 in auto-inflammatory diseases has progressed greatly in the last 20 years, from the initial identification of IL-17 to the recent demonstration of clinical benefits with antibodies against IL-17 and IL-23p19 in psoriasis, AS, RA, and multiple sclerosis.[20] T_H17 cells have been identified as a separate lineage from T_H1 and T_H2 cells. T_H17 differentiation can be driven by transforming growth factor beta (TGFβ) and IL-6 via the IL-17+ lineage-specific transcription factor RORγt, which eventually promotes chronic inflammation and autoimmunity.[21] However, the differentiation of T_H17, iT_{reg}, and T_H1 lineages has been found to overlap, such that early retinoic acid and IL-2 signalling and late IL-23 or IL-12 signalling can deviate T_H17 differentiation towards iT_{reg} and T_H1, respectively (Figure 1). This flexibility in T_H17 levels may have some relevance in inflammatory diseases such as axSpA.[22]

The differentiation, growth, stabilisation, and development of T_H17 effector memory cells involve a range of signalling molecules including IL-1β, IL-6, IL-23, and IL-21. As well as the IL-17 family of cytokines, fully mature T_H17 cells produce IL-21, thus positively feeding back to promote the development of further T_H17 cells. Moreover, T_H17 cells express the chemokine receptor CCR6, which responds to the ligand CCL20 that is present in inflamed joints in axSpA.[21]

IL-17 is not only produced by classical adaptive immunity T_H17 cells in lymphoid organs, but is also produced by cells in several other organs and at sites of inflammation.[20] Natural immunity T_H17 cells in the skin and mucosal tissues express IL-17 in response to IL-1 and IL-23. Group 3 innate lymphoid cells in the gut and skin, and γδT cells in mucosal and peripheral tissues produce IL-17 in response to dectins, IL-1, IL-23, and Toll-like receptor signalling, whereas the γδT cells in the lymphoid organs produce IL-17 in response to IL-1, IL-23, and T-cell receptor signalling. Invariant natural killer (NK) cells in the liver require CD1 and glycolipids to express IL-17.

Susceptibility to AS is largely genetically determined – studies with identical twins estimate heritability to be >90%.[23] The identity of the environmental trigger in most cases of AS is likely to be something very common. The progression of the disease, including the rate of ankylosis, also has a genetic component, with the heritability of radiographic severity estimated at 62%.[24]



The factors identified in red indicate those that deviate the T_H17 developmental programme towards iT_{reg} early (retinoic acid and IL-2) or T_H1 late (IL-23 or IL-12)

Figure 1: Flexibility: Overlap of the T_H17, iT_{reg}, and T_H1 axes of differentiation.
IL: interleukin; TGFβ: transforming growth factor beta; IFNγ: interferon gamma; RA: retinoic acid.

Approximately 25% of the genetic loci involved in the heritability of AS have been identified.[25] Among these, human leukocyte antigen B27 (HLA-B27) accounts for 20% and IL-17 pathway genes around 0.5% of cases.[25] It is thought that these molecules are interconnected, as HLA-B27 is linked to the IL-17 pathway both through NK cell activation[26] and the unfolded protein response (UPR) (Figure 2).[27,28]

Several theories have been proposed to explain the role of HLA-B27 in the pathogenesis of AS. While it is a classical antigen-presentation molecule, there is no strong evidence for an 'arthritogenic' peptide that would be presented to T cells by HLA-B27. Instead, the formation of HLA-B27 heavy chain homodimers on the cell surface may activate IL-17-producing immune cells through NK receptors. Misfolding of HLA-B27 and its subsequent accumulation in the endoplasmic reticulum (ER) may also be involved, leading to a UPR, potentially involving endoplasmic reticulum aminopeptidase 1 (ERAP1), which is also linked to the IL-17 pathway.

Cytokines that upregulate HLA-B27 expression may trigger UPR activation under conditions where HLA-B27 misfolding reaches a critical threshold. This in turn could polarise cells such as macrophages to increase production of IL-23 relative to IL-12. In susceptible individuals with permissive (non-protective) IL-23 receptor genotypes, this may promote T_H17 activation over T_H1, thus inducing IL-17 production and inflammation.[29] It is hypothesised that abnormal innate immune responsiveness to either infection or biomechanical stress can trigger this pathway from HLA-B27 to IL-17.[26] AS may, therefore, be considered an auto-inflammatory disease rather than a strictly autoimmune disease.

Several genetic loci contributing to other rheumatic diseases such as psoriasis and PsA also affect the T_H17 pathway, including IL-23, IL-12, and ERAP1.[30] Indeed, IL-23 and IL-17 can be considered unifying factors in such disorders.[31] IL-23 sensitivity is associated with AS, PsA, and inflammatory bowel disease (IBD), and IL-23 overproduction is associated with SpA (e.g. IL-13 production in psoriasis, HLA-B27 misfolding in IBD, and subclinical ileitis in 70% of SpA patients without IBD).[31]

Evidence is accumulating for the involvement of the IL-17/IL-23 pathway in axSpA, supporting a scenario in which a genetic susceptibility leads to IL-23 overproduction in response to stress and a variety of responsive cells release IL-17-related cytokines that results in the inflammation, osteoproliferation, and skin inflammation seen in spondyloarthritis. IL-23-responsive cells (expressing IL-23 receptor) have been found at the tendon/bone interface in a mouse model, in which overproduction of IL-23 caused periosteal and entheseal pathology similar to that seen in patients with spondyloarthritis.[32] Studies in patients with axSpA and AS have also found increased levels of IL-17-producing cells.[33-35]

In summary, IL-17-producing T_H17 cells in the immune system are involved in inflammatory diseases. Gene polymorphisms in the IL-17 signalling pathway, HLA-B27 misfolding, and IL-17/IL-23 pathways have a role in the pathogenesis of axSpA. There are many cellular sources beyond T_H17 cells that contribute to IL-17 production in spondyloarthritis. In preclinical models of spondyloarthritis, the IL-17/IL-23 pathway mimics clinical spondyloarthritis, including inflammation and bone formation.

Recent Advances in Current and Emerging Treatments

Professor Dominique Baeten

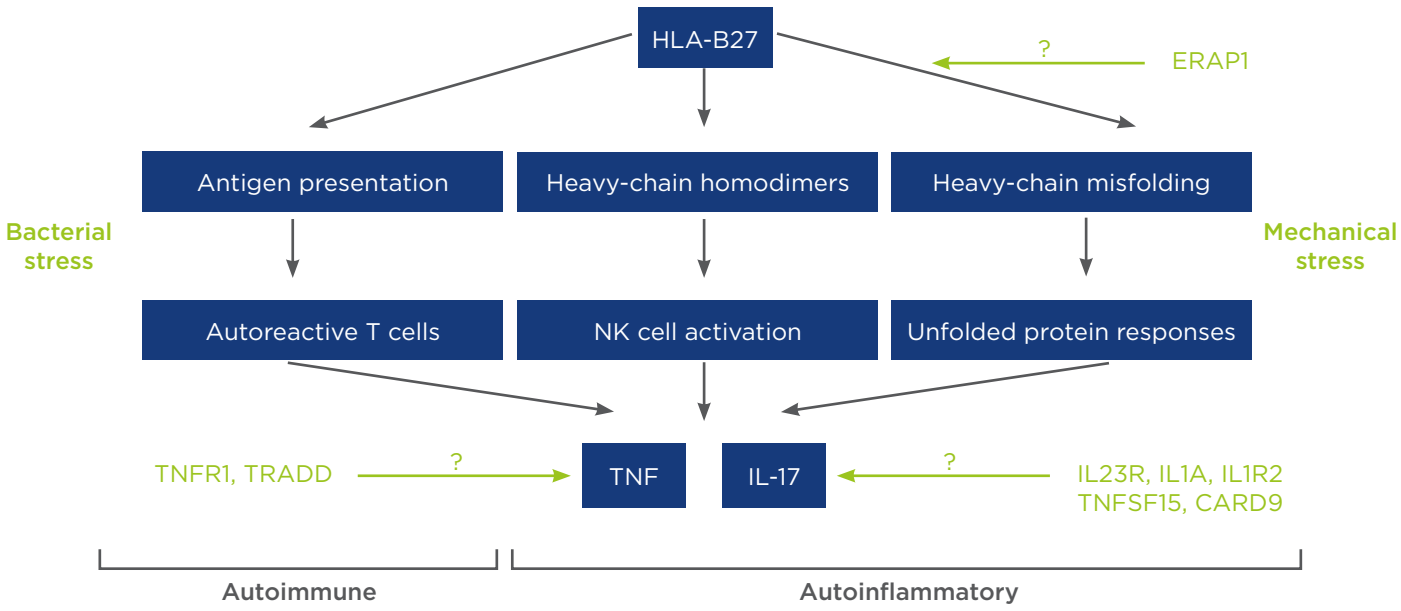
The current standard of care for AS is NSAIDs and local corticosteroid injections as first-line therapy, accompanied by non-pharmacological treatments including education, exercise, physical therapy, rehabilitation, patient associations, and self-help groups. If high disease activity continues, anti-TNF therapy, which has shown good clinical responses in terms of signs and symptoms of inflammation in patients with AS, is the standard second-line treatment.[11-15]

Historically, diagnosis of AS and implementation of therapy were often delayed, in many cases by several years.[36] However, the Assessment of SpondyloArthritis International Society (ASAS) has recently developed new criteria for classification aimed at promoting an earlier and more effective diagnosis and treatment of AS and nr-axSpA (patients with signs and symptoms of axial disease who lack the radiographic damage to the sacroiliac joints to meet the modified New York criteria).[37] As demonstrated in the RAPID-axSpA study, certolizumab pegol was an effective treatment for

patients with AS and those with non-radiographic axSpA.[15] Other trials have shown good responses to anti-TNF therapy in other manifestations of SpA.[38] Patients with AS often present with a range of symptoms, including arthritis, tendinitis, IBD, uveitis, spondylitis, and psoriasis, and it is important that all of these manifestations are treated.

Overall, it is estimated that approximately one-third of patients treated with TNF inhibitors are good responders; another one-third benefit from the treatment but may still experience some signs and symptoms (moderate response); and another one-third are non-responders (or intolerant). Rapid relapse after interruption of treatment, no clear impact on osteoproliferation, and no alternative biologic treatments are among the remaining unmet clinical needs in axSpA.

Abatacept is a fusion protein that selectively binds to CD80 and CD86 receptors on antigen-presenting cells.[39] In this way, abatacept inhibits T cell activation, selectively blocking the specific interaction of CD80/CD86 receptors with CD28 and, therefore, inhibiting T cell proliferation and B cell immunological response. In a prospective, open-label pilot Phase II study conducted to explore the short-term efficacy and safety of abatacept in patients with active AS as an alternative to anti-TNF therapy, no response was observed in TNF inhibitor-naïve patients or patients with inadequate response to TNF inhibitor.[40] No evidence of significant efficacy has also been found with a range of other therapies in Phase II studies in AS, including rituximab (anti-CD20 monoclonal antibody [mAb]), IL-6 and IL-1 blockade, and apremilast (PDE-4 inhibitor), while ustekinumab (IL-12/IL-23 inhibitor) has shown some efficacy in a proof-of-concept study. While there are a number of targets currently under investigation, including IL-17A, new treatment options are urgently required for AS. Secukinumab and ixekizumab are two anti-IL-17 mAbs in clinical development for the treatment of AS, PsA, and/or psoriasis (Table 1). Clinical development of brodalumab, an mAb against IL-17RA, is currently on hold.



'Stress' hypothesis: inflammation is induced by abnormal innate immune responsiveness to mechanical or bacterial danger signals.

AS is an autoinflammatory but not an autoimmune disease.

Figure 2: Potential roles of HLA-B27 in spondyloarthritis.

AS: ankylosing spondyloarthritis; ERAP1: endoplasmic reticulum aminopeptidase 1; HLA-B27: human leukocyte antigen B27; IL: interleukin; NK: natural killer; TNF: tumour necrosis factor; TNFR1: tumour necrosis factor receptor 1; TRADD: tumour necrosis factor receptor 1-associated death-domain protein; TNFSF15: tumour necrosis factor superfamily member 15; CARD9: caspase recruitment domain-containing protein 9.

Table 1: IL-17 blockade in human immune-mediated inflammatory diseases.

Drug	Mechanism	Clinical status
Secukinumab	Fully human anti-IL-17A mAb	Licensed for psoriasis In development for AS and PsA
Ixekizumab	Humanised anti-IL-17A mAb	In development for psoriasis and PsA
Brodalumab	Fully human anti-IL-17RA mAb	Development on hold

AS: ankylosing spondylitis; IL: interleukin; PsA: psoriatic arthritis; mAb: monoclonal antibody.

With two large Phase III trials (MEASURE 1 and MEASURE 2) completed, secukinumab is the anti-IL-17 agent most advanced in its clinical development.[41,42] In this symposium, only the results from MEASURE 1 were discussed. During the MEASURE 1 trial, patients (n=371) were randomised to intravenous (IV) secukinumab 10 mg/kg (Weeks 0, 2, and 4) followed by subcutaneous secukinumab 150 mg or 75 mg every 4 weeks, or matched placebo. Baseline demographics and disease characteristics were well-balanced across treatment groups, and a large proportion of patients were anti-TNF-naïve (approximately 73% in each group).[41]

Significant improvements in the proportion of patients achieving ASAS20 criteria were observed with secukinumab IV-75 mg and IV-150 mg versus placebo after 16 weeks of treatment, with responses sustained through Week 52. At Week 16, ASAS20 response rates were 59.7% and 60.8% with secukinumab IV-75 mg and IV-150 mg, respectively, versus 28.7% with placebo ($p<0.0001$). The onset of response was fast, with most patients responding after 1 or 2 weeks of treatment. During the initial 16 weeks, all predefined primary and secondary endpoints were achieved with both doses of secukinumab. Improvements in ASAS20 response rates at Week 16 with secukinumab versus placebo were observed regardless of prior exposure to anti-TNF agents.[41] Secukinumab also produced rapid and sustained improvements in patient-reported outcomes, including quality of life.[42,43] The efficacy of secukinumab has been also demonstrated in other subtypes of spondyloarthritis.[38]

Secukinumab had a good safety profile in MEASURE 1. The incidence of adverse events was lower in the active treatment groups compared with placebo.[41] Over the entire treatment period, the incidence (number of cases per 100 patient-years) of malignant or unspecified tumours was 0.9 with secukinumab IV-150 mg and 0.4 with secukinumab IV-75 mg versus 2.4 with placebo. Adverse events of interest included *Candida* infections (3 non-serious cases that did not lead to discontinuation) with no signals for invasive infections, neutropaenia (3 cases of Grade 3 and 1 case of Grade 4), and Crohn's disease (3 cases [0.8%; 75 mg] in patients with a history of this disease or with predisposing factors).

In summary, anti-TNF therapies are currently the only biologic therapy for AS. A significant unmet need remains, particularly for patients who have an inadequate response or intolerance to anti-TNF therapy. IL-17A inhibition with secukinumab is effective in patients with AS, with benefits observed regardless of prior anti-TNF exposure. Several outstanding questions remain regarding IL-17 inhibition in AS, including: the long-term efficacy and safety of IL-17 inhibitors; whether they can have an impact on structural damage, and their efficacy in other subtypes of AS; where such agents should be positioned in the AS treatment algorithm in comparison with anti-TNFs; which are the most appropriate patients for treating with IL-17 inhibitors; and whether this is the optimal way to target the IL-23/IL-17 axis or whether other specific targets, such as p40, p19, IL-17A/F, IL-17R, or RORC, would be more effective.

The Imaging Perspective: The Effects of IL-17A Inhibition on Bone Inflammation and Damage

Doctor Xenofon Baraliakos

The natural course of AS, untreated with biologics, shows progression from an initial presentation

of chronic back pain, indistinguishable from any other causes of back pain, to inflammation, bone erosion and, ultimately, ankylosis of the spine over several decades with associated pain and functional disability. During the course of the disease, the structural changes characteristic of AS, such as sacroiliitis[44] and formation of syndesmophytes, can be detected by radiography but by this time it is too late for treatments to halt the progression of the disease.

Over the last 15 years, the use of biologic anti-TNF therapies has been effective in reducing the clinical symptoms of AS, and patients' pain and disability. Magnetic resonance imaging (MRI) of bone oedema to measure inflammation objectively has similarly shown a reduction of inflammation in response to anti-TNF treatments in the long and short-term.[45-47] The effect of anti-TNF therapies on inflammation can potentially have an effect on bone formation in AS. It has been shown that inflammation is linked to new bone formation in the spine in AS,[48] but more recent studies have identified an intermediate stage in which a reduction of inflammatory activity is linked with the development of fatty lesions in subchondral bone marrow.[49] In sites where inflammation had occurred, fatty lesions developed and bone formation was seen more frequently and more rapidly at these sites. Identification of these fatty lesions by MRI could potentially provide an earlier point in the sequence to diagnose and treat progression of AS.

Although anti-TNF therapies such as etanercept, infliximab, and adalimumab have been shown to be effective in reducing the signs and symptoms and improving the quality of life in patients with active AS over 2 years, no significant inhibition of radiographic progression was observed.[50-52] The search for additional treatments is now focussing on other targets in the inflammatory cascade. Successful attempts to treat AS patients have been made with IL-23 and IL-17 inhibition. The preclinical results published by Sherlock et al.[32] in 2012 offer a rationale for the efficacy of this approach. IL-23-responsive cells were identified in a mouse model of enthesitis; these produced IL-17 with subsequent inflammation and tissue damage in response to increased IL-23.[32] This inflammation was reduced by anti-IL-17 treatment.

The potential similarity between the enthesitis model and clinical AS led to a proof-of-concept study of IL-17A inhibition with secukinumab, which included an MRI sub-trial with an open-label extension to investigate whether an imaging response could be observed in addition to a clinical response. The trial showed a rapid clinical response to secukinumab at 28 weeks, which was sustained at 94 weeks. MRI of the vertebral edges showed decreases in inflammation from baseline in the secukinumab arm compared with the placebo arm at 94 weeks. Furthermore, there was no change in the amount of fatty lesions in the patients treated with secukinumab.[53] Structural progression and inflammation were also assessed by MRI imaging in the Phase III MEASURE 1 trial.[41] The Berlin scoring system for bone marrow oedema was used for objective assessment of inflammation. A rapid response in terms of a reduction from baseline in the sacroiliac joint total oedema score was seen in both secukinumab arms at 16 weeks (a change of –1.05 for secukinumab 75 mg and –1.30 for secukinumab 150 mg versus –0.17 for placebo; both $p<0.01$). This was sustained at 52 weeks. A similar response was seen with MRI of the spine at 16 weeks (a change of –2.53 for secukinumab 75 mg and –1.08 for secukinumab 150 mg versus –0.55 for placebo; $p<0.01$ and not significant, respectively). These results confirm that IL-17A inhibition can reduce inflammation in both the spine and sacroiliac joint.[54]

In conclusion, anti-TNF therapies do not inhibit radiographic progression over 2 years of treatment. The IL-17 pathway may play an important role in the pathogenesis of structural damage in AS and thus offers a promising target for new treatments. MRI data demonstrate that IL-17A blockade with secukinumab provides early and sustained reductions in spinal inflammation in both sacroiliac joints and the spine. Further data are required to explore the effects of IL-17 blockade on radiographic progression.

Summary

Axial spondyloarthritis is a relatively common disease that is often poorly managed. Current treatment guidelines recommend NSAIDs as the first-line therapy for axSpA, followed by TNF blockade in patients with high disease activity or with inadequate response. Pharmacological treatments should be accompanied by non-pharmacological therapies that involve education, exercise, physical therapy, rehabilitation, patient associations, and self-help groups. Significant

unmet needs and treatment challenges remain, particularly for patients who have an inadequate response or intolerance to anti-TNF therapy. Opportunistic infections and other complications are among the barriers to providing effective treatment with currently available anti-TNF therapies.

IL-17 has emerged as a central player in the pathogenesis of SpA and thus may be an effective target in axSpA. Promising data are emerging from the use of agents neutralising IL-17 such as secukinumab and ixekizumab. While MRI techniques have demonstrated that IL-17 blockade with secukinumab provides early and sustained reductions in spinal inflammation in both sacroiliac joints and the spine, further data are required to explore the effects of IL-17 blockade on radiographic progression. Finally, several outstanding questions remain regarding IL-17 inhibition in AS, including where such agents should be positioned in the AS treatment algorithm, their impact on structural damage, and whether there is an optimal way to target the IL-23/IL-17 axis.

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