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Title:

The advent of IL-17A blockade in ankylosing spondylitis: secukinumab, ixekizumab and beyond

Abstract

Introduction: Secukinumab, an interleukin-17A (IL-17A) antagonist, is the first non-TNF alpha inhibitor agent licenced for ankylosing spondylitis (AS), which opens up a new era of alternative cytokine targets beyond TNF.

Areas covered: This review explores the pathophysiology and scientific evidence behind the use of this new mode of action and discusses the basis for its efficacy and clinical utility in the management of AS. In particular, how the emergent data points towards the efficacy of secukinumab and ixekizumab, a second emergent IL-17A blocker, in AS has helped focus research into the IL-23/17 axis in entheseal driven disease in man and how IL-17A inhibition may be linked to the presence of innate and adaptive immune cell populations capable of IL-17A elaboration in these target tissues.

Expert commentary: Collectively these emergent data point towards an efficacious role of IL-17A inhibition strategies targeting AS pathogenesis in a fundamental way whilst carrying a good safety profile.

Keywords

Interleukin-17 inhibitors, IL-17 inhibition, IL-17A blockers, ankylosing spondylitis, axial spondyloarthritis, axSpA, secukinumab, ixekizumab, brodalumab.

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that predominantly affects the axial skeleton causing chronic spinal pain and stiffness, reduced range of movement, structural damage and adversely impacts on quality of life. AS represents the typical radiographic form of axial Spondyloarthritis (axSpA) with an estimated prevalence of 0.5-1%[1]. The overall prevalence of axSpA, including the non-radiographic (nr-axSpA) and radiographic (AS) forms of the disease, is not well defined but varies in the region of 0.32 to 1.4% dependent on ethnicity and geography[2]. Additionally, the burden of long-term disease resulting from post inflammation new bone formation and specifically spinal ossification causes permanent functional limitation. Peripheral joint disease, enthesitis and extra-articular manifestations such as uveitis and underlying inflammatory bowel disease, the latter often subclinical, are well described and shared by the clinical spectrum of disease within SpA.

Historically, AS therapies have been limited to mainly physiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs). In the last two decades, major therapeutic progress has been made with the advent of the TNF inhibitor (TNFi) biologic drugs, which have produced a huge impact on patient outcomes and substantially ameliorated AS in many patients. Despite the availability of several TNFi therapies for AS, there is still a need for alternative modes of action particularly as up to 40% of AS patients do not demonstrate a meaningful clinical response to TNFi[3,4]. Further, TNFi may be contraindicated for certain patients and given the lack of efficacy of conventional

disease modifying anti-rheumatic drugs (cDMARDs) for axial symptoms in AS, the need for an additional class of biologic was overdue[3,5–7].

Interleukin-17 (IL-17) and its receptor were first identified in 1993 and through translational research this discovery paved the way for the development of commercially available IL-17A inhibitors. Six isoforms of IL-17 designated from A to F have been described but it is IL-17A and then IL-17F that have the biggest role in inflammatory disease[8]. Initially IL-17 was discovered through murine lymphoid cells from a product of the CTLA8 gene obtained from human and mouse genomes[9]. The initial experimental understanding of IL-17 focused on CD4 IL-17A elaborating T –cells "Th17 cells" in autoimmune diseases with a rheumatological focus in the rheumatoid arthritis arena, which has not come to fruition[10,11].

Secukinumab, a fully human recombinant IgG1 kappa monoclonal antibody that is a selective antagonist to IL-17A was successful in phase 3 clinical trials, initially for psoriasis (PsO) and psoriatic arthritis (PsA) closely followed by studies in AS[7,12]. However, secukinumab failed in trials in RA, thus indicating that this pathway is key to SpA related arthropathy. These observations led to the prompt development of other drugs targeting the IL-17 pathway[13–15]

One of the most pertinent questions in AS is whether structural damage caused by bone ossification or new bone formation and measured as radiographic progression can be prevented. In recent years it has been shown that TNFi may lead to a 50% reduction in the odds of radiographic progression if treated early, compared with worse radiographic outcomes for longer untreated disease[16]. The rate of progression appears to be variable with presence of syndesmophytes at baseline in the spine accounting for a fourfold increase when compared with patients without[17]. Therefore, assessment of

future disease modification through suppression of IL-17A and alternative pathways in SpA is still of great interest to further understand longer term effects on spinal ossification and how it can be prevented. This review will provide an update on secukinumab, the first licensed IL-17A inhibitor in AS, and emergent phase 3 study data from ixekizumab, another IL-17A blocker.

2. IL-17 in the pathogenesis of AS

IL-17 is an inflammatory cytokine involved in defence against bacterial and fungal infections. IL-17 also contributes to chronic inflammation and appears to have a pivotal role in SpA, particularly AS, PsO, and PsA[18]. IL-17 mediated inflammation has been strongly conceptualised in terms of the upstream cytokine, IL-23 with the resultant IL-23/IL-17 axis driving disease (figure 1). IL-23 is primarily produced by antigen presenting cells such as macrophages and dendritic cells and along with other cytokines including IL-1 and IL-6, it promotes the polarization to IL-17 expressing cells.

IL-17 was first thought to be secreted by CD4+ T cells but is now known that IL-17 is also produced by lymphocytes of both the adaptive and innate immune system, including T helper-17 cells (Th17), IL-17- producing CD8+T cells (Tc17), γδT cells and type 3 innate lymphoid cells (ILC3)[19,20]. These cells can also release several other cytokines including IL-21, IL-22, IL-23, TNFα, and IL-17F, depending upon the stimulus[21].

There are single nucleotide polymorphisms (SNPs) in the IL-23 receptor (R) gene which are strongly implicated in the IL-23/IL-17 axis in AS[22]. These genetic polymorphisms to the IL-23 receptor have been shown to correlate with susceptibility for the development of AS and could potentially play a significant role in the induction of Th17 cells[23].

Furthermore, it was found that the IL23R R381Q gene variant is protective against IL-23 induced tissue pathologies[24]. This gene selectively attenuates IL-23 induced Th17 cell effector function, without any intrusion on Th17 cell differentiation. Genetic variations of genes in the IL-23 signalling pathway and their influence on Th17 cell effector function in patients with AS and SpA have also been described in other studies[25]. AS patients also have more IL-23+ cells in the subchondral bone marrow when compared to controls[26]. However, no correlation is seen between IL-23R polymorphism and serum IL-17 levels in AS patients[27]. Genome wide association studies have identified *TRAF3IP2 SNPs* on chromosome 6q21 as a susceptibility locus for PsA and PsO with this gene coding for the ACT1 protein that is involved in IL-17 receptor A (IL-17RA) signalling[28]. Whole exome sequencing and refining of SNPs has located rs4819554 at the G minor allele of the IL-17RA promotor region of AS patients which is associated with functional severity (Bath Ankylosing Spondylitis Functional Index or BASFI) and may be a good biomarker of disease severity[22].

At the tissue and cellular level, current knowledge in disease mechanisms in AS relates to poly-enthesitis, including adjacent spinal vertebral osteitis at the human axial skeleton, with a secondary synovitis at the synovio-entheseal complex or diseased peripheral joints[29]. The strong HLA-B27 association with AS incriminates the major histocompatibility class I (MHC-1) pathway in disease pathogenesis[30]. Such MHC-1 molecules expressed on virtually all cells and most notably permit T lymphocyte screening and detection of foreign proteins, in turn allow the removal of infected or transformed cells by cytotoxic CD8 T cells[31]. The epistatic interaction between HLA-B27 and the ERAP-1 gene which trims peptides prior to HLA class 1 presentation certainly supports the idea that peptide presentation to CD8 T cells is important in disease

pathogenesis[32]. Such primed CD8 T cells are capable of the production of IL-17A and are termed "Tc17 cells"[33].

Experimental animal models or human data have thus far failed to firmly incriminate CD8+ T cells as the key pathogenic drivers in AS but the genetic evidence for CD8 T cell involvement is growing[34]. It is known that HLA-B27 alone is not enough to cause disease and alternative models have been considered including the presence of HLA-B27 homodimers on the cell surface resulting in misfolding and the formation of these HLA-B27 homodimers at the cell surface to trigger IL-23 and IL-17 production[35]. Macrophages from HLA-B27 positive AS patients may secrete increased IL-23, which is thought to be independent of protein misfolding associated stress[36]. In HLA-B27 transgenic rats there is upregulation of IL-17 after Th17 cell development[37]. It is also known that overexpression of IL-23 in a murine model can reproduce a SpA like disease with enthesitis and new bone formation[38]. In this model, disease was dependent on IL-23 inducing IL-17 in resident population of γδT cells[27]. These γδT cells have also been recently described in the healthy human enthesis[39]. Another murine model showed that during local inflammation, γδT cells expressing IL-17 accumulate at the enthesis, aortic valve, and ciliary body[40]. The ciliary body is particularly relevant given propensity of AS for uveitis. There is much less data on the human enthesis but a recent study has shown that the normal spinal enthesis soft tissue and bone contains a population of resident type 3 innate lymphoid cells that are capable of IL-17 production[41]. Furthermore, the expansion of type 3 innate lymphoid cells (ILC3s), producing IL-17 and IL-22, has also been shown at the bone marrow, synovial fluid and peripheral blood of patients with AS[42].

Once secreted, IL-17 triggers the stimulation of macrophages, fibroblasts, epithelial and endothelial cells initiating the release of pro-inflammatory chemokines and cytokines such and TNFα, IL-6 and IL-1[35]. More specific for AS is the fact that IL-17A facilitates osteoblastic differentiation and proliferation therefore promoting bone formation and regeneration[43]. Therefore, the inhibition of IL-17A, although not proven, is anticipated to have effects on halting radiographic progression in AS[44].

There is a sizeable body of evidence connecting the gut microbiome with intestinal inflammation, and both the IL-17/23 axis and HLA-B27 have been implicated as key factors in the pathogenesis of AS and axSpA. Interestingly, IL-17A serves a protective function in maintaining the integrity of the intestinal barrier and is involved in gut epithelial cell proliferation and healing[45]. But unlike antibodies to IL-23 which have shown improvement in signs and symptoms of inflammatory bowel disease, neutralizing IL-17 causes disruption to the intestinal barrier and atypical macrophage subpopulations causing exacerbation of colitis[46,47].

3.0 Secukinumab in AS

3.1 Efficacy

The first study to evaluate the efficacy of secukinumab in AS was a randomised double-blind, proof of concept study[48]. Secukinumab was administered with intravenous (i.v) loading doses given (10mg/kg) at baseline and at 3 weeks with an assessment at week 6 for the primary efficacy endpoint as the percentage of patients with a 20% response in line with the Assessment of SpondyloArthritis international Society criteria for improvement (ASAS20)[48]. Figure 2 outlines the ASAS definition and the domains assessed. An ASAS 20 response was obtained in 59% of patients treated with

secukinumab (n= 23) compared with 24% (n= 6) that received placebo[48]. A serious adverse event which was the development of a *Staphylococcus aureus* subcutaneous abscess occurred in one case in the secukinumab treated group.

Subsequently, secukinumab has been evaluated in four randomised controlled double-blind phase 3 clinical trials named MEASURE 1, 2, 3, and 4 respectively. Eligibility criteria required participants to fulfil the modified New York criteria (mNY) for AS and have evidence of active disease as shown by a BASDAI (Bath Ankylosing Spondylitis Disease Activity Score) and spinal visual analogue score (VAS) equal of greater than 4. In the first study (MEASURE 1) 371 patients were randomised to receive secukinumab with i.v loading doses at 10mg/kg at baseline, week 2 and week 4 followed by 150 mg or 75mg every 4 weeks by subcutaneous (s/c) injection, or alternatively placebo only starting at week 8[7]. Patients in the placebo arm were reassigned to either secukinumab 75mg or 150mg every 4 weeks at Weeks 16/24 based on clinical response. In the second study, participants (n = 219) were randomised to either secukinumab s/c 150 mg or 75mg weekly or placebo, given at baseline,1,2,3, and then every 4 weeks starting at week 4[7]. At week 16, patients in the placebo group were randomly reassigned to s/c secukinumab at a dose of 150 mg or 75 mg. At 16 weeks in MEASURE 1, ASAS20 responses rates were 61% (150mg), 60% (75mg) compared with 29% for placebo demonstrating significance between drug and placebo ($p<0.001$). For MEASURE 2 the primary endpoint was achieved with an ASAS20 response of 61% (150mg) and 41% (75mg) compared with 28% for placebo ($p<0.001$). There were improvements seen for the secondary endpoints in both studies including for ASAS40 response rates (figure 3). It is noteworthy that 26% and 39% of patients were TNFi inadequate-responders (TNF-IR), respectively, in first and second trials, and at 16 weeks the ASAS20 and ASAS40 response rates were higher for TNFi naïve compared to

TNFi-IR[7]. In MEASURE 2, 59% of the TNFi-IR achieved an ASAS20 response by 52 weeks compared with 82% for TNFi naïve at the 150mg secukinumab dose using the last observation carried forward method[49,50]. Figure 4 compares the ASAS20 responses in TNFi naïve vs TNFi-IR from MEASURE 2 study. Following 2 years of subcutaneous therapy with secukinumab, trial data shows that there is sustained improvement in the same clinical outcomes for both 150mg and 75mg secukinumab doses[50].

In the MEASURE 3 study, participants (n=226) were randomised to placebo (n=74) or secukinumab given via initial IV loading doses at 10 mg/kg (baseline, weeks 2 and 4) followed by subcutaneous secukinumab 300 mg (n=76) or 150 mg (n=74) every 4 weeks, or matched placebo (n=76) starting at 8 weeks[51]. At week 16, patients in the placebo group were re-randomized to receive s/c secukinumab 300 mg or secukinumab 150 mg every 4 weeks. At 16 weeks in MEASURE 3, ASAS20 responses were at 60.5% ($p<0.01$) with 300mg of secukinumab and 58.1 % ($p<0.05$) in the 150mg treatment group, compared with 36.8% for placebo and achieving the primary endpoint. Furthermore, ASAS40 responses were also modest at 42.1% and 40.5% for respective secukinumab doses compared with 21.1% for placebo. Both subgroups (TNFi naïve and TNFi-IR (76% vs 24% of the population respectively) demonstrated successful improvements in the primary (ASAS20) and secondary endpoints (ASAS40, hsCRP, ASAS5/6, BASDAI, and ASAS partial remission)[51].

Long term clinical efficacy was maintained at weeks 52 in 86.0%, and 83% of patients respectively in both MEASURE 1 and 2 trials[7]. Results from the fourth randomised controlled trial MEASURE 4 , assessing long-term efficacy safety and tolerability of secukinumab, demonstrated that treatment was completed by 97% of patients at 16 weeks and 83% at 2 years of secukinumab therapy[52]. However, the

primary endpoints assessed by ASAS20 responses were not achieved (p=0.057 (loading); p=0.054 (no loading dose). ASAS20 responses were sustained up to 16 weeks but also beyond the placebo controlled period up to 2 years and importantly the safety profile matched that of the previous studies [52]. There is longer term 3 year efficacy data from the MEASURE 2 study which demonstrated sustained efficacy with 86% and 76% of patients in the treatment group completing week 156 on secukinumab 150mg and 75mg doses respectively[53]. At 3 years, these patients were able to achieve sustained ASAS20/40 (70.0%, 61%) outcomes matched by 1 year ASAS20/40 outcomes (74%/57%) respectively[53].

The current licensed dose of secukinumab for the treatment of AS is 150mg administered via subcutaneous injection at weeks 0, 1, 2, 3, 4 (loading) and every 4 weeks thereafter[7,48]. It is noteworthy that in the clinical trials, there were significant dosing differences in PsO and PsA compared with AS, with two doses commercialised, 300mg and 150mg in PsO/PsA, the former dose recommended in PsA for TNFi failures or ongoing active disease, with only 150mg dose available for AS, including for TNFi failures. This raises the question as to why 150mg in AS should be as equally effective as 300mg in PsA? Whether it is due to the body mass index (BMI) of PsA cases being potentially higher, or whether both diseases have intrinsic differences to IL-17A inhibition or whether some AS cases will actually respond to higher dosing needs further consideration.

3.2 Safety

There was a higher incidence of infection in the MEASURE 1 and 2 studies compared to placebo 30% and 32% versus 12% and 27% respectively[7]. The exposure adjusted

incidence of serious adverse events was 8.0 and 8.6 per 100-patient years for secukinumab 150mg and 75mg groups respectively in MEASURE 1, and 6.6 and 7.7 per 100-patient years for MEASURE 2. The most frequent side effects were nasopharyngitis, headache, diarrhoea, upper respiratory tract infections and candida. The corresponding incidences were 17.9, 8.3, 8.1, 8.0, and 0.9 per 100-patient years respectively from both studies (pooled). The incidence of grade 3 or 4 neutropenia was 0.7 events per 100 patient years. A total of 3 patients (MEASURE 1 and 2) suffered major cardiac adverse events including one fatal myocardial infarction (MI; MEASURE 2), thought to be unrelated to the study drug which was continued. The pooled adjusted incidence rate of cardiac events was 0.4 events per 100-patient years. There was also one death in a patient in the placebo group of MEASURE 1 as a result of depression and suicide[7]. One patient developed a stroke in the first study. In both studies, there were a total of 5 cancers reported which included a B cell lymphoma, breast cancer, transitional cell carcinoma of the bladder, malignant melanoma and lymphoma which resulted in the discontinuation of treatment in all patients.

There were no cases of *Mycobacterium tuberculosis* (TB) reactivation and pooled data from five other studies in patients with latent or active TB suggest that IL-17 inhibition shows no evidence of increased TB infections[54]. In contrast to TNF inhibition, this may be an important consideration in geographical regions of high TB prevalence. This also mirrors the Mendelian disorders of IL-17 pathway where fungal infection rather than TB is the rule[55]. There was no significant increase in risk of bacterial or fungal infections in the clinical trials and the overall infection risk appears to be similar to TNF inhibition which has also been demonstrated against etanercept in head to head phase 3 trials for PsO[52,56].

In contrast to other biologic drugs such as the TNFi class [57] there have been no reports to date of demyelinating disease with secukinumab or IL-17A inhibitor induced systemic lupus. Secukinumab has been used successfully in lupus nephritis complicated by psoriasis vulgaris[58,59]. Going forward, registry data on secukinumab will inform about long term safety with respect to rates of malignancies and other toxicities.

Anti-secukinumab antibodies were detected in 2 patients on 150mg dose in MEASURE 1 study, neither of which developed any loss of ASAS20 response at 2 years[60]. No antidrug antibodies were detected in the MEASURE 2 study at 2 years.[50] Further data will be needed for more accurate assessments of the safety risks likely to come from registry data in the future.

3.3 Radiographic progression

Despite being very effective for clinical manifestations of AS, the current scientific literature on TNFi suggests limited inhibition of radiographic progression in established AS including where syndesmophytosis is already present[61,62]. The disease process in AS involves both new bone formation, through osteoblast activation, as well as osteoclast activation from inflammation resulting in longer term bone loss[63]. The theory that TNFi may lead to accelerated new bone formation has not been substantiated by continuous TNFi over 8 years where the overall rate of new bone formation in AS is not increased[64,65]. There does not appear to be a difference in effect based upon the TNFi dose either, as shown by golimumab treated patients who do not have an increase in ossification even when standard (50mg) and higher (100mg) doses are used[61]. Interestingly, it has been shown that the strongest predictors of new bone formation are fatty and inflammatory MRI changes[66]. Although the role of inflammation on new bone

formation is not fully understood, outcomes appear better in patients without baseline syndesmophytes and less inflammation where less radiographic progression is observed[61,67]. More reassuringly, recent data from the Swiss registry have reported that TNFis do inhibit spinal radiographic progression following 10 years of observation[68].

In MEASURE 1, lateral lumbar and cervical radiographs were conducted at baseline and 2 years and were scored using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) method. The mean change in mSASSS from baseline to 2 years was 0.30 (standard deviation (SD) 2.53)[60] and in 95% of patients with no syndesmophytes there were no additional syndesmophytes at 2 years. In those with baseline syndesmophytes, 70% remained free of additional syndesmophyte development at 2 years[60]. Longer term data are needed to understand the effects of TNF and IL-17 inhibitors on radiographic progression in AS. Given that the closely related IL-22, a cytokine linked to new bone formation in vivo and in vitro, is not blocked by secukinumab, the emergent data are very reassuring[38,69].

3.4 Enthesitis

Entheses are sites of attachment to bone which include ligament and tendon insertions and inflammation at these sites forms a key part of the pathophysiology in AS and PsA[70]. AS is often regarded as polyenthesitis of the spine. Assessment of peripheral enthesitis was not specifically evaluated in the MEASURE studies even though peripheral enthesitis may be a significant problem in AS[71]. However, there are data from clinical trials for secukinumab in PsA. Data from the FUTURE 2 study demonstrated that for the 300mg dosage, 27/56 (48.2%) enthesitis resolved at 24 weeks on secukinumab versus

placebo 14/65 (21·5%) (p-value 0.0025)[72]. There was a mean change in the Leeds enthesitis index at week 16 at -1.7 (SD 1.8). In the largest phase 3 randomised placebo controlled double blind trial in PsA, FUTURE 5, 996 patients with active PsA were recruited to receive secukinumab with a loading dose (300mg or 150mg), without loading dose (150mg) or placebo[73]. It is noteworthy that concomitant methotrexate therapy was permitted in the study and enthesitis was present in a total of 60.4% of patients. Of these patients, 55.7% (300mg with s/c loading dose) and 54.6% (150mg with s/c loading dose) demonstrated resolution of enthesitis by week 16, compared to 35.4% for placebo, and 41.9% (150mg) without loading doses[73]. The primary endpoints of the trial were met (American College of Rheumatology 20 criteria or ACR20), and secondary endpoints were significant including for enthesitis and dactylitis for either 300mg or 150mg with loading doses, and not significant at 150mg without the loading dose. Therefore, similar to the efficacy shown with the TNFis, IL-17A blockade does appear to be effective for peripheral dactylitis and enthesopathy at 300mg or 150mg s/c provided initial s/c loading doses are administered.

3.5 Extra articular manifestations of AS

3.5.1 Psoriasis

There is good evidence for the efficacy of secukinumab in psoriasis from both dermatology trials and in PsA. The results from a phase 3 trial (ERASURE) confirmed efficacy of secukinumab for both doses, 300mg and 150mg each with s/c loading doses, compared to placebo. At week 12, a PASI 75 (75% or more improvement in the psoriasis area-and-severity index score) was achieved in 81.6% and 71.6% compared

with 4.5% for placebo[56]. Another trial (FIXTURE) demonstrated superiority of secukinumab, with a PASI 75 of 77.1% (300mg) and 67% (150mg), compared to etanercept (44%) or placebo (4.9%) therefore achieving its secondary endpoints for both comparators ($p<0.001$)[56]. The most recent FUTURE 5 study also reported good PASI 75 responses of 70% and 60% for 300mg and 150mg with s/c loading doses respectively ($p<0.05$ for both) compared to 12.3% for placebo and 58.1% for 150mg without a loading dose[73]. Similarly, the PASI 90 responses were also significant. These data therefore indicate that secukinumab is a good option particularly for patients with AS who have skin psoriasis.

3.5.2 Crohn's Disease

The phase 2 study of secukinumab in Crohn's disease (CD) was associated with non-efficacy or even occasional worsening of disease[74]. Given the link of AS and SpA with subclinical IBD, this might have been a potential harbinger of adverse outcomes in AS and PsA. However only a few cases of CD developed from the AS and PsA clinical trials including for the entire safety reporting period, CD developed in one patient in the treatment group and re-occurred in two patients with a previous CD history compared with no cases in the placebo arms for MEASURE 1. In MEASURE 2, there was one new case of CD developed and another patient with a prior history developed a re-occurrence[7]. In the FUTURE 5 studies in PsA, development of CD occurred in only one patient with a prior colitis history receiving 150mg (without loading) and another with new onset ulcerative colitis (150mg with loading) reported as serious adverse events[73]. One other case of mild, non-serious CD occurred which was resolved prior to the time of reporting. Given the data already known suggesting many active cases of AS have

subclinical IBD, then the fact that very few cases of IBD developed or were exacerbated using this IL-17A blocking strategy is somewhat reassuring.

3.5.3 Uveitis

In MEASURE 1 and 2, uveitis was observed in 6 patients receiving secukinumab, (5/6 with a previous history) and 2 on placebo(1 with prior history), with only one case reported as a serious adverse event in the 150mg group in MEASURE 1 and similarly one new case of uveitis occurred on 150mg secukinumab in MEASURE 2 with all cases having continued study treatment[7,50]. There is a lack evidence for the efficacy of this strategy in anterior uveitis, though phase 3 studies for adalimumab in non-infectious panuveitis were associated with lower risk of uveitis flare[75]. There have been three randomised controlled trials (RCTs) for non-infectious uveitis including Behçet's uveitis, non-Behçet's with active uveitis and quiescent non- Behçet's uveitis but the primary endpoints of these studies were not met[76]. Crucially, 31 patients enrolled with active non-infectious, non- Behçet's uveitis (INSURE study) were randomised to receive secukinumab at any of three different dosing regimens or placebo did not show any difference on mean change in vitreous haze score in the study eye between the treatment and placebo groups. No patients completed the study which was terminated due to non-achievement of the primary endpoints and therefore closed by the sponsor[76]. However, in Behçet's uveitis treated with TNFi (adalimumab) there is some four year follow up data indicating that there is an excellent retention rate of 77% at 12 months and 64% at 48 months of follow up[77]. Co-treatment with other DMARDs did not show any statistically significant difference in retention rates. Bearing in mind that all these studies did not specifically assess HLA-B27 positive or AS associated uveitis, there

remains an area of unmet need to determine the safety of whether one may switch a patient from TNFi to IL-17A blockers with a prior history or in the presence of severe uveitis. Caution should be applied in this area and more data is needed in the uveitis and IBD domain.

4.0 Ixekizumab and other IL-17 inhibitors

4.1 Efficacy in PsA and psoriasis (PsO)

Other IL-17A blockers have recently emerged including ixekizumab, which has slightly different pharmacodynamics from secukinumab and demonstrated efficacy in PsO in phase 3 clinical trials, and showed superiority over etanercept and placebo[15]. The data from the SPIRIT-P1 trials for ixekizumab in PsA were also very promising demonstrating a 20% improvement in the ACR20 with responses of 69.1% (80mg, fortnightly) and 68.8% (160mg, 4 weekly) at 24 weeks with sustained responses at 1 year[78]. Similarly the SPIRIT-P2 also demonstrated efficacy for ixekizumab fortnightly and monthly dosing[14]. Further data are also expected from other agents such as brodalumab, a fully human IL-17 receptor antagonist to the IL-17A homodimers, IL-17A/F heterodimers, IL-17E and possibly IL-17C. It has a different mode of action in comparison to secukinumab and ixekizumab since brodalumab acts downstream of IL-17A by targeting the IL-17 receptor. Initial clinical trials in PsO were terminated due to increased suicidal ideation, but causality was not shown and the development programme was reinstated. Brodalumab, was investigated for PsO in two Phase 3 trials (AMAGINE) and demonstrated superior PASI75 responses compared to placebo, and superior PASI100 responses compared to ustekinumab[79]. It became licensed for the treatment of skin psoriasis first in the US and Japan and then in Europe. From the PsA

point of view, the (AMVISION-2) phase 3 clinical trial for brodalumab in PsA has been completed and results are awaited[80].

4.2 Enthesitis and Dactylitis

The data from the SPIRIT-P2 study in PsA demonstrated improvements in both dactylitis and enthesitis as measured by the Leeds dactylitis index-basic (LDI-B) and the Leeds enthesitis index (LEI) respectively[14]. For ixekizumab at the 4 weekly dose (IXEQ4W) regimen, there was an improvement in the LDI-B in 21/28 (75%) at week 24 as compared with PBO 3/14 (21%) with a p-value of 0.002 by Fisher's exact test. Although successful for dactylitis, statistical significance was not achieved for enthesitis. At week 24 there were 24/68 (35%) patients (IXE Q4W, p=0.08) and 26/84 (31%) patients (IXEQ2W, p=0.27) achieving the LEI as compared with 15/69 (22%) for PBO. The success in dactylitis identified through LDI-B maps to the known class effect of this mode of action. However, unlike the clinical trials for PsA, clinical trials for ixekizumab and secukinumab in AS did not specifically evaluate enthesitis and dactylitis, despite the strong association of enthesitis in AS.

4.3 Efficacy in AS

Data from the two phase 3, double-blind randomised controlled trials for ixekizumab in AS, COAST-V (NCT02696785) and COAST-W (NCT02696798), have just emerged[13,81]. Both studies assessed the efficacy of ixekizumab in the treatment of active AS utilising the ASAS40 response at 16 weeks as their primary outcome. The study populations differed in that COAST-W included subjects who had experienced a prior inadequate

response or failure to one or two TNFi drugs, whereas COAST-V comprised of a treatment naïve population. The primary endpoints were achieved in both of these trials demonstrating significant ASAS40 responses for ixekizumab for two different dosing regimens, every two or every four weeks. The respective ASAS40 and ASAS20 responses are outlined in figure 5. An impressive 52% and 48% achieved an ASAS40 response at the 80mg two weekly and four weekly doses respectively in TNFi-naïve patients (COAST-V) compared with 18% for placebo[13]. Statistically significant differences were also found in TNF-IR patients (COAST-W) with 30.6% and 25.4% achieving ASAS40 responses for respective doses (80mg Q2W and 80mg Q4W), however there was no significant improvement observed from the initial loading dose of 160mg[81]. Significant improvements were observed for the secondary outcomes in both studies including ASAS20 responses, the mean change from baseline in MRI of the sacroiliac joint and spine SPARCC scores, and mean change from baseline in the CRP [13,81]. COAST-V also demonstrated significant BASDAI50 responses[13]. Similarly at 16 weeks in COAST-W, disease activity improved with statistical significance for change in baseline ASDAS and BASDAI scores, and achievement in ASDAS <2.1 (low disease activity or inactive disease), and physical function significantly improved as measured by change from baseline BASFI [81]. Both studies also demonstrated statistically significant quality of life outcomes as measured by the SF-36 PCS (36-item short form survey physical component summary). Further data from COAST-W is likely to be available in the future as part of its 1 year extended treatment period and optional 2 year extension trial.

4.4 Safety

The trials assessing ixekizumab, COAST-W and COAST-V, similar to the MEASURE trials with secukinumab. also showed increased infection rates but these were lower than previous trial data for ixekizumab in PsO and PsA[78,81,82]. The treatment emergent adverse events from ixekizumab therapy were most commonly nasopharyngitis and upper respiratory tract infection in the COAST-V trial and nasopharyngitis and injection site reactions in COAST-W[13,81]. Only one serious adverse event was seen in each of the ixekizumab treatment groups in COAST-V, with gastroenteritis (IXE Q2W) and urinary tract infection (IXE Q4W), and appendicitis in the adalimumab group[13]. There were no reports of tuberculosis, or anaphylaxis in either study. In COAST-W, one patient (IXE Q4W) developed acute promyelocytic leukaemia who possessed a genetic risk factor (PML-RARA mutation) for this disease and another patient with a prior history of depression committed suicide deemed unrelated to therapy (IXE Q2W) by the blinded investigator[81]. Although fungal infection might be expected with IL-17A blockade, there were no reports of such for ixekizumab in COAST-V, except one case in the adalimumab treated parallel group[13].

4.5 IBD and anterior uveitis

One patient was subsequently recorded as having treatment emergent Crohn's disease by the clinical events committee after receiving four doses of ixekizumab Q2W, having previously had a history of NSAID-induced colitis[13]. In COAST-W, IBD was reported in one patient in the placebo group (1%, colitis, prior IBD history), no patients in IXE Q2W group and three patients in the IXE Q4W group (2.6%, 1 colitis, 1 ulcerative colitis, 1 Crohn's) two of which were new cases but with history of smoking, previous abdominal pains in one case and previous anaemia in another[81].

Treatment emergent anterior uveitis was reported in one patient with a previous history (IXE Q4W) in COAST-V, and for COAST-W five patients were reported (two IXE Q2W, three IXE Q4W), all with longstanding disease, three with a previous history of anterior uveitis and 4/5 positive for HLA-B27[13,81].

5. Expert Commentary

The current body of clinical trial data shows that IL-17A inhibition is efficacious in the treatment of AS. The MEASURE trials with secukinumab and COAST trials with ixekizumab showed ASAS20 and ASAS40 responses comparable to responses seen with the TNFis[83]. Despite these good responses, further research is required to accurately determine whether IL-17A blockade shows the same pattern of response as TNFi or whether it has a superior effect on radiographic progression. For dactylitis, both drugs demonstrated efficacious outcomes, but for enthesitis only secukinumab at 300mg and 150mg dosages demonstrated successful outcomes in clinical trials for PsA. The head-to-head trial data for psoriasis suggests that TNF blockade with etanercept is not as effective as IL-17A blockade with secukinumab, which would therefore appear a more suitable option in concomitant AS with psoriasis. Efficacy of IL-17A inhibition in extra-articular manifestations and especially inflammatory bowel disease has not been demonstrated which favours using TNFi in such cases. Despite similar head-to head trial data for ustekinumab versus etanercept in PsO, ustekinumab does not have a license for AS and studies in AS were discontinued due to non-achievement of primary or major secondary endpoints over placebo (NCT02437162)[84]. These observations may reflect data from some experimental models that suggest IL-23 has a role in the

initiation of SpA but is not required for the continuation of disease[85]. Further support for this comes from a new IL-23 inhibitor, risankizumab, which fell short in phase 2 studies in AS with no meaningful improvement and failure to achieve the primary endpoint[86]. However, head-to-head data for the IL-17 blockers and other biologics specifically in AS is lacking. The IL-23/12 inhibitors are now licensed for the treatment of Crohn's disease but were not successful for AS[87]. To date, it has not been determined whether the higher posology and loading doses in Crohn's may actually exhibit benefit in axial disease.

With regards to uveitis, the available data, although limited, would encourage strong caution in the use of IL-17A inhibition in subjects with a history of severe uveitis.

Significant ASAS40 and ASAS20 responses in AS demonstrated by ixekizumab maps to similar efficacy as secukinumab both being IL-17A inhibitors. However, compared to the higher dose of secukinumab (150mg compared to 75mg) no significant incremental increase in efficacy was observed for the higher dose of ixekizumab (80mg every 2 weeks compared with the 80mg every 4 weeks) which possibly may relate to the high affinity of the drug[88]. In the same way the intravenous loading doses of secukinumab, trialled (MEASURE 4 study) did not significantly change the efficacy outcomes in AS either[52]. The emerging ixekizumab data for the enthesitis and dactylitis outcomes also support the scientific rationale of targeting IL-17A and we anticipate further data in the longer term. The rates of IBD and anterior uveitis development, with secukinumab and ixekizumab, suggest that TNFi is the preferred treatment strategy in the presence of these extra-articular manifestations. Longer term safety data are needed given the relatively new arrival of this drug in PsO and PsA and recent clinical trial data in AS.

Recent real life reports show that secukinumab has also been tried in the synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome with improvement in 2 out of 3 patients after 3 months of therapy[89]. Successful treatment of another rare psoriatic disease variant, acrodermatitis continua of Hallopeau, has also been reported with secukinumab[90].

However, there are still some aspects of these and other immunotherapies that remain elusive to the clinician, such as the paradoxical psoriasis or SpA that may occur with immunotherapy for IBD[91]. Indeed, in contrast to its efficacy in PsO and AS, paradoxical PsO and psoriatic spondyloarthritis reactions to secukinumab have also been reported[92–94]. Further data are required to further understand these paradoxical manifestations with IL-17A blockade.

6. Five-year view

How then, will IL-17 blockade shape the next 5 years? Increasing use of secukinumab is to be expected over the next years given its license for AS which permits a non-TNFi choice of biologic therapy for clinicians in treating patients with AS. Similarly, Ixekizumab is expected to enter this arena, given the positive clinical trial efficacy data that has emerged in AS, with further data to come from the extended trial period. Both secukinumab and ixekizumab provide a choice of IL-17A targeted blockade and it is anticipated that registry data on the longer term safety follow up of AS patients will emerge in the near future. In the interests of preventing ankylosis, we are hopeful that data on radiographic progression with ixekizumab arises in the future and more data for both of these drugs. Further studies assessing secukinumab (NCT02696031) and

ixekizumab efficacy, COAST-X (NCT02757352), may broaden the scope of IL-17A inhibition as they target non-radiographic axial SpA[95,96].

Whereas an initial phase 2 trial for brodalumab in axial SpA (NCT02429882) was cancelled and withdrawn at the time of the reports of suicidal ideation in the trials for PsO, there is a phase 3 clinical trial of brodalumab vs placebo (NCT02985983) in non-radiographic axSpA underway[97,98], and its results are eagerly awaited given the unique mode of action.

Further antibodies are in development including bimekizumab, a monoclonal dual IL-17A and F blocker with data in phase 2b clinical trials (NCT02963506), and bispecific antibodies targeting both IL-17A and TNFα (COVA322) in phase 1/2 trials[99,100]. The future development of nanobodies, which are camel or llama derived single domain antibody fragments consisting of heavy chain antibodies with full antigen binding capacity is an interesting prospect forthcoming[101]. Probably further into the future beyond 5 years, we anticipate the advent of fynomers, small binding proteins that are engineered to target molecules with similar affinity to monoclonal antibodies which creates an exciting prospect of novel immuno-biotherapeutics[102].

Key issues

- The IL-23/17 axis plays a crucial role in the pathogenesis of AS.
- IL-17A at the intestinal barrier serves as protective, but more data are needed for how that translates into clinical manifestations from IL-17A blockade. Few cases of IBD developed from clinical trials with secukinumab and ixekizumab.

- Data from the MEASURE 1-3 studies in AS have demonstrated efficacy for secukinumab in TNFi naïve and inadequate responders (TNF-IR).
- ASAS 20 and 40 responses compare equally for doses 150mg (MEASURE 1/2) or 300mg (MEASURE 3) irrespective of i.v or s/c loading doses.
- Secukinumab and ixekizumab have demonstrated improvements in outcomes for psoriatic arthritis including for enthesitis, dactylitis and psoriasis which are also associated with AS.
- Good safety data is available for secukinumab and ixekizumab and there are no cases of reactivation of TB with secukinumab from pooled data which may point to use of IL-17A blockade over TNFi in areas of high TB prevalence.
- Longer term data in AS are required to assess the effects of secukinumab and ixekizumab on radiographic progression, drug survival and safety including the caution in inflammatory bowel disease and AS associated uveitis.
- IL-17A blockers should be considered as a treatment for AS in either TNFi naïve or TNFi experienced patients or when TNFis are contraindicated.
- Other IL-17 inhibitors such as brodalumab and bimekizumab are being investigated in AS.

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