SUPPLEMENT

Effect of IL-17A blockade with secukinumab in autoimmune diseases

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ABSTRACT

Genetic studies and correlational expression data in diseased tissues have pointed to the role of interleukin (IL)-17 and Th17 cells in the pathogenesis of autoimmune disorders such as psoriasis, inflammatory bowel disease and seronegative spondyloarthropathies. Th17 cells are known to produce the proinflammatory cytokine IL-17A as well as other effector cytokines, including IL-17F and IL-22. Recent research has demonstrated that IL-17A is also expressed by multiple lineages of the innate immune system, including mast cells, neutrophils, dendritic cells, γδ-T cells, macrophages and natural killer cells. It can thus be expected that the inhibition of IL-17A as a therapeutic target in autoimmune disease would exert different physiological effects than the suppression of Th17 cell activity. Early clinical data are now available on secukinumab (AIN457), a recombinant, highly selective, fully human monoclonal antibody (mAb) secukinumab, which specifically targets the IL-17A cytokine, in early clinical trials in psoriasis, rheumatoid arthritis (RA), autoimmune uveitis, psoriatic arthritis (PsA), AS and Crohn’s disease (CD) will be reviewed. Although the focus here will be on secukinumab as an example, results with other investigational agents that target IL-17A and the Th17 pathway (ixekizumab, brodalumab and ustekinumab) will also be compared and contrasted.

INTRODUCTION

The interleukin-17 (IL-17)/IL-17 receptor (IL-17R) family has recently been discovered to have a potentially important role in the pathogenesis of human autoimmune diseases. Much of the enthusiasm has been based on the discovery of T helper 17 (Th17) cells and the genetic association of IL-17 with autoimmune diseases such as psoriasis, inflammatory bowel disease and ankylosing spondylitis (AS). However, even before the discovery of Th17 cells, studies implied a role for the cytokine IL-17 subtype A (IL-17A), by which Th17 cells are characterised, in inflammatory arthritis.1 2 Several antibodies that target IL-17A signalling directly or indirectly (via IL-17R or IL-23, which is necessary for Th17 cell expansion) are in clinical development for the treatment of autoimmune diseases (table 1). Differences among these molecules (eg, binding affinity and specificity, isotype, Fc region mutations) have potential implications for their safety and efficacy. This article will provide an overview of the role of IL-17A in autoimmune diseases. Effects of the fully human monoclonal antibody (mAb) secukinumab, which specifically targets the IL-17A cytokine, in early clinical trials in psoriasis, rheumatoid arthritis (RA), autoimmune uveitis, psoriatic arthritis (PsA), AS and Crohn’s disease (CD) will be reviewed. Although the focus here will be on secukinumab as an example, results with other investigational agents that target IL-17A and the Th17 pathway (ixekizumab, brodalumab and ustekinumab) will also be compared and contrasted.

IL-17A: ROLES IN IMMUNITY AND AUTOIMMUNE DISEASE

IL-17A is a dimeric glycoprotein with biological functions that bridge innate and adaptive immunity.3 4 In the circulation, the IL-17A cytokine exists as either a homodimer of two IL-17A chains or a heterodimer with IL-17F. IL-17A and IL-17A/F bind to a receptor complex comprised of the IL-17RA and IL-17RC subunits, albeit with different affinities for each subunit.3 5 IL-17RA and IL-17RC are members of a newly discovered family of cytokine receptors (figure 1) that mediate signalling through a distinct pathway that depends on Act1 (also known as CIKS (Connection to IKK and SAPK/JNK)), resulting in the activation of proinflammatory mediators typically associated with the innate immune response, such as IL-1, IL-6, tumour necrosis factor (TNF) and IL-8.6 10 IL-17A is thought to play an important role in innate responses against infection, triggering proinflammatory signalling and promoting neutrophil recruitment to rapidly attack extracellular pathogens.11 The relevance of IL-17 in host defence has been demonstrated in recent genetic studies of subjects with chronic mucocutaneous candidiasis disease.12 In this syndrome characterised by recurrent or persistent infections (predominantly with Candida albicans or to a lesser extent Staphylococcus aureus) of the mucosae, nails and skin in the absence of other autoimmune or infectious manifestations,13 candidate gene sequencing of two subjects identified mutations in IL-17F or in the IL-17 receptor chain IL-17RA. Interestingly, the phenotype of these IL-17-deficient patients is thus far limited to susceptibility to a small number of organisms in a specific anatomic distribution; the possibility of impaired responses to other infections cannot be excluded. Of note, no isolated mutations in IL-17A resulting in overt immunodeficiency have been identified to date. Recent studies of autoimmune disorders demonstrate that IL-17A is expressed by multiple lineages...
of innate immune cells, including mast cells, neutrophils, dendritic cells, γδ-T cells, macrophages and natural killer cells.14 Abundant IL-17A-producing mast cells, neutrophils and γδ-T cells, for example, have been identified in psoriatic skin lesions,15–17 a finding confirmed by our examination of psoriatic plaque tissues (figure 2). Peripheral blood neutrophils from patients with systemic lupus erythematosus have exhibited enhanced IL-17 production.18 Further, IL-17A-producing mast cells and neutrophils are evident in the inflamed synovial tissues of RA and AS patients.19 20 Factors regulating the synthesis and release of IL-17A by innate immune cells in these autoimmune diseases remain the subject of active investigation.

IL-17A is also produced by cells of the adaptive immune system. Th17 cells generate IL-17A and other cytokines (eg, IL-17E; IL-22) that act on IL-17 receptor-bearing tissue cells, such as keratinocytes, synoviocytes, fibroblasts and epithelial cells. Activation of these cells induces the production of cytokines that recruit additional Th17 cells, as well as innate cells such as neutrophils, and leads to the production of antimicrobial factors involved in host defence against microbial infection.21 Dysregulation of Th17 cells plays a role in autoimmune disorders; increased numbers of these cells have been demonstrated in the lesions of conditions such as psoriasis, multiple sclerosis and CD.22–25

IL-12 and IL-23 (a member of the IL-12 cytokine family) play important roles in shaping T cell immune responses, including those involving Th17 cells. IL-23 and IL-12 are heterodimeric ligands that share the common β-chain p40 subunit.26 IL-12 and IL-23 drive Th1 and Th17 polarisation, respectively, and thus the corresponding Th1-associated and Th17-associated inflammatory and autoimmune responses (figure 3).27 IL-23 stabilises the Th17 phenotype in an autocrine fashion28 and directly promotes production of IL-17.29 Polymorphisms in genes encoding IL-12p40 and IL-23R have been associated with psoriasis, inflammatory bowel disease and seronegative spondyloarthropathies.14 30

From a therapeutic standpoint, agents that target IL-17A act selectively at the level of a key effector cytokine (figure 1), thereby preserving other immune functions of IL-17A-expressing cells.
This selectivity contrasts with numerous other strategies. IL-23/12 inhibitor therapies are believed to block the generation and maintenance of Th1 and Th17 cells, thereby impacting numerous T-helper activities beyond IL-17A (figure 4). Similarly, IL-17R inhibitors, by acting at the level of a shared cytokine receptor, block the signalling of multiple members of the IL-17 cytokine family (eg, IL-17F, IL-25 and possibly others). Beyond the IL-17A-targeting approaches, TNFα is a pleiotropic cytokine that activates multiple immune cell types. Accordingly, TNFα inhibition also carries the potential for broad immune modulatory effects. Small molecule Janus-associated kinase inhibitors can block cytokine signal transduction. However, Janus-associated kinase signalling is a ubiquitous pathway that is involved in signalling from many different types of cytokine receptors and is not specific to immune cells.

Figure 2 Immunohistochemistry of skin biopsies: innate immune cells are present in psoriatic tissue and stain positive for IL-17. Immunofluorescent co-staining* of mast cells (marker/red: MCT) and neutrophils (marker/red: MPO) for IL-17 expression (green) using human psoriasis skin tissue sections confirms data by others and indicates that innate cells such as neutrophils and mast cells are capable of producing IL-17. IL, interleukin; MCT, mast cell tryptase; MPO, myeloperoxidase. *IL-17/MPO co-stainings: The staining was performed on formalin fixed paraffin embedded human psoriasis skin tissue sections. Polyclonal goat anti-IL-17 (R&D AF-317-NA, Lot: AB10411041) in green (donkey anti-goat Alexa488). Polyclonal rabbit anti-MPO (Abcam ab45977) in red (chicken anti-rabbit Alexa594). IL-17/MCT staining: polyclonal goat anti-IL-17 (R&D AF-317-NA, Lot: AB10411041) in green (donkey anti-goat Alexa488). Monoclonal mouse anti-MCT, Clone AA1 (Dako M07052) in red (chicken anti-mouse Alexa594). Data on file Novartis.
The first therapeutic evidence that Th17 cells and consequently IL-17A might be involved in the pathogenesis of human autoimmunity came from studies of ustekinumab, an anti-IL12p40 antibody that inhibits IL-12 and IL-23, in psoriasis.\textsuperscript{36,37} The evidence is indirect, however, as IL-12/23 inhibitors affect the Th1 and the Th17 pathways.

Clinical data on agents that directly target IL-17A or its receptor are now available. Secukinumab (AIN457), a highly selective, fully human immunoglobulin G1k (IgG1k) mAb directed against the IL-17A cytokine, has been evaluated in multiple autoimmune diseases, including psoriasis, RA, CD, PsA, AS and autoimmune uveitis. Ixekizumab, a humanised IgG4 anti-IL-17A mAb, and brodalumab, a fully human IgG2 anti-IL-17RA mAb, are also in clinical development and have shown efficacy in autoimmune disease.

**Psoriasis**

In a series of phase II studies,\textsuperscript{38–41} in moderate to severe psoriasis, secukinumab demonstrated a favourable safety and tolerability profile with robust clinical activity, including improvements in psoriasis area and severity index (PASI) scores and investigator global assessment scores. A single infusion of secukinumab (3 mg/kg) resulted in rapid and sustained improvement of psoriasis symptoms in a double-blind, placebo-controlled, parallel-group, phase IIA proof-of-concept (POC) study (N=56).\textsuperscript{38} At week 4, 83% of secukinumab patients versus 11% of placebo patients achieved significant decreases from baseline in investigator global assessment score categories (p=0.0004). Secukinumab was associated with an early significant reduction from baseline in mean PASI score compared with placebo (58% vs 4%; p=0.0001) (figure 5). These effects were maintained through 12 weeks.\textsuperscript{38} Consistent with the...
significant decrease in skin inflammation that was evident clinically, molecular profiling of psoriatic skin samples following treatment with secukinumab showed selective modulation of cytokines, including IL-12B, IL-17A, IL-17E, IL-21, IL-22, IL-26, interferon (IFN)-γ, chemokine (C-C motif) ligand 20 and TNE. These molecules are expressed by leukocyte and by tissue lineages, pointing to a diverse impact of IL-17A on multiple cellular lineages involved in psoriasis pathophysiology.

Secukinumab was further evaluated in phase IIB subcutaneous (SC) dose-ranging and SC and intravenous (IV) regimen-finding studies. A randomised, double-blind, parallel-group, placebo-controlled, phase IIB SC dose-ranging study evaluated four SC doses of secukinumab in 125 patients. Secukinumab 150 mg and 75 mg (each administered at weeks 0, 4 and 8) were associated with significantly greater rates of PASI 75 response at week 12 compared with placebo (81% and 57% vs 9%; p<0.001 and p=0.002, respectively, for the two comparisons). Rates of adverse events (AEs) and serious AEs (SAEs) were comparable between secukinumab and placebo cohorts.

On the basis of the findings indicating the safety and efficacy of SC secukinumab 150 mg, a placebo-controlled phase IIIB trial was conducted to assess three regimens of SC secukinumab 150 mg in 404 patients with moderate to severe plaque psoriasis. Secukinumab ‘Early’ (weeks 0, 1, 2 and 4) and ‘Monthly’ (weeks 0, 4 and 8) induction regimens resulted in significantly greater rates of PASI 75 response at week 12, the primary efficacy endpoint of the study, versus placebo (55% and 42% vs 2%; p<0.001 for both comparisons). As in the dose-ranging study, secukinumab was associated with a safety profile comparable to placebo.

A similar phase IIB regimen-finding study was conducted to evaluate IV secukinumab induction regimens. All secukinumab IV induction regimens were associated with significantly greater rates of PASI 75 and 90 responses at week 12 compared with placebo. Although there were six SAEs in the secukinumab treatment cohort, none were considered by the investigators to be drug-related.

The safety and efficacy of ixekizumab were evaluated in a double-blind, placebo-controlled phase IIA study, in which 42 patients were randomised to treatment with two doses of SC secukinumab 10 mg/kg, given 3 weeks apart, or placebo. The primary efficacy endpoint, versus placebo (70 mg, 45.0%; 140 mg, 85.9%; 210 mg, 86.3%; 280 mg, 76.0%; placebo, 16.0%; p<0.001 for all comparisons). Despite strong early responses with brodalumab, assessments at week 16 (6 weeks after the final dose of brodalumab) showed a loss of response in all dosing groups, with decreases in mean percentage of PASI improvement, rates of PASI 50–100 responses and other efficacy endpoints. Overall, the brodalumab-treated groups exhibited higher percentages of patients who experienced AEs (68%–82%) compared with the placebo-treated group (62%).

To date, there have been no head-to-head comparative trials of anti-IL-17A and anti-IL-17RA monoclonal antibodies in psoriasis, and comparisons based on results from separate studies should be made cautiously and only after the phase III studies, when the number of patients is larger and the final dose and regimen of each molecule is known. Results from the phase II dose-finding studies of secukinumab, ixekizumab or brodalumab described above, however, do suggest an early and pronounced therapeutic response of similar magnitude with each agent.

This observation is consistent with the mechanism of action of IL-17A-based therapies, which rapidly inhibit the cytokine directly or via receptor blockade, rather than modulating IL-17A activity via effects on the turnover and activity of Th17 cells. Overall, the magnitude of response with IL-17A inhibitors appears at least as high or greater than that reported for existing therapies. The proportions of PASI 75 responders with secukinumab (up to 81%), ixekizumab (up to 83%), and brodalumab (up to 82%), compare favourably with the probability of PASI 75 response ascertained in a meta-analysis of data on agents including infliximab (81%), adalimumab (71%), etanercept (50%), methotrexate (42%) and cyclosporine (53%). Data from large-scale clinical trials are needed before any definitive conclusions can be drawn.

### Psoriatic arthritis

The safety and efficacy of secukinumab in PsA were evaluated in a double-blind, placebo-controlled phase IIA study, in which 42 patients were randomised to treatment with two doses of SC secukinumab 10 mg/kg, given 3 weeks apart, or placebo. The primary endpoint, was 59% with secukinumab compared with 23% for placebo, and the difference was not statistically significant (p=0.27). Rates of ACR20 responses at weeks 12 and 28 for secukinumab were 59% and 43%, respectively, and for placebo, 15% and 18%, respectively. Secukinumab was associated with a reduction in median C reactive protein (CRP) level from baseline to week 6 (from 5.0 mg/L to 3.8 mg/L). There was an increase in median CRP from baseline to week 6 (from 5.9 mg/L to 15.2 mg/L), with placebo. Secukinumab was also associated with reductions in erythrocyte sedimentation rate.

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**Figure 5** Reduction in PASI score with secukinumab: week 0 through week 12. Clinical response to secukinumab in patients with chronic plaque psoriasis. Patients received a single intravenous infusion of secukinumab (3 mg/kg). Values are mean±SE. PASI, Psoriasis Area and Severity Index; mg, milligram; kg, kilogram. Reprinted with permission from AAAS: Science Translational Medicine 2:52ra72, copyright 2010.
Rheumatoid arthritis

A phase II A, first-in-human, POC study was conducted to assess the safety, tolerability, pharmacokinetics and clinical activity of single or multiple doses of secukinumab (10 mg/kg highest dose) in patients (N=52) with RA. Secukinumab 10 mg/kg given at baseline and week 3 resulted in a significantly greater ACR20 response rate at week 6 versus placebo (46% vs 27%; p=0.12 (statistical significance set a priori at the p<0.2 level)). Responses to secukinumab were rapid and durable. The proportion of secukinumab-treated patients with an ACR20 response reached 50% by week 4 (compared with 51% for placebo; p=0.15) and continued above 50% through week 16 (54% for secukinumab vs 51% for placebo; p=0.08) (figure 6). Secukinumab was also associated with significant reductions versus placebo in 28-joint disease activity scores (DAS28) and CRP values over time. AEs occurred at a higher rate with secukinumab (81%) compared with placebo (65%).

Long-term results from another phase II study of secukinumab have demonstrated the durability of responses in RA. In a placebo-controlled, double-blind study, 237 patients with active RA were randomised to four different monthly SC doses of secukinumab (25 mg, 75 mg, 150 mg, 300 mg) or placebo. The primary efficacy endpoint was the rate of ACR20 response at week 16. Patients with responses to secukinumab remained on the same dose, while patients without responses (except those receiving the 300-mg dose) were dose-escalated at week 20. All patients originally assigned to placebo were switched to secukinumab 150 mg. Patients were followed through week 52. In the first part of the study, rates of ACR20 responses at week 16 were higher for the three highest secukinumab dosing groups versus placebo (75 mg, 47%; 150 mg, 47%; 300 mg, 54%; placebo, 36%). However, these differences in response rates did not reach significance. Among week 16 secukinumab responders who remained on the secukinumab 150 mg dose (n=20), rates of ACR20 response at 24 and 52 weeks were 75% and 90%, respectively, and rates of ACR70 response at weeks 24 and 52 were 20% and 40%, respectively. In this same group of responders to secukinumab 150 mg, the rate of remission by European League Against Rheumatism criteria (ie, a score of ≤2.6 points on the DAS28-CRP) increased over time: 30% at week 24 and 40% at week 52. There were no unexpected safety concerns.

No effect of secukinumab was found in an analysis of lipid parameters and indices of atherogenic risk.

Results from both of these phase II studies support a role for IL-17A in the pathogenesis of RA and are consistent with findings from a POC study of the humanised IL-17A mAb ixekizumab (LY2439821) in RA. In this study, the rate of ACR20 response with the highest dose of IV ixekizumab (2.0 mg/kg) was significantly greater at week 10 compared with placebo (90% vs 56%; p≤0.05). The tolerability profile of ixekizumab appeared to be favourable, with the majority of AEs mild to moderate in severity. A phase II study of multiple SC doses of ixekizumab also yielded evidence of efficacy in RA. In the randomised, double-blind study, RA patients who were receiving concomitant disease-modifying antirheumatic drugs and were either naïve to biological therapy (n=260) or resistant to TNFα-inhibitor therapy (n=188) received placebo or ixekizumab 5 mg, 10 mg, 30 mg, 80 mg or 180 mg at weeks 0, 1, 2, 4, 6, 8 and 10. As indicated by logistic regression analysis, there was a significant (p=0.051) dose-response relationship in ACR20 response among biological-naïve patients at week 12 (primary study endpoint). Meaningful differences versus placebo in ACR20 response at week 12 were seen for ixekizumab 50 mg, 80 mg and 180 mg in biological-naïve patients and for ixekizumab 80 mg and 180 mg in those resistant to TNFα-inhibitor therapy. Significant improvements in DAS28-CRP versus placebo were seen for all ixekizumab doses in the biological-naïve group and the group refractory to TNFα-inhibitor therapy, with a rapid onset of efficacy within 1 week after the first dose. The frequency of treatment-emergent AEs was similar across all treatment arms.

Results from phase II studies with two different anti-IL-17A compounds support a role of IL-17A in the pathogenesis of RA. A therapeutic effect was evident, with the proportion of ACR20 responders ranging from 47% to 54% at week 16 with secukinumab (vs 31% to 36% with placebo) and 40%–70% at week 12 with ixekizumab (vs 23% to 35% with placebo). Data from large-scale clinical trials are needed to determine the magnitude of efficacy that can be expected from IL-17A inhibitors and consequently the place of these agents in treatment relative to other biologics.

Autoimmune uveitis

Secukinumab was evaluated for the treatment of autoimmune uveitis in an open-label POC pilot study, in which 16 patients with non-infectious uveitis refractory to local or oral corticosteroids received two infusions of secukinumab (10 mg/kg) at baseline and 3 weeks. The disease severity of patients with posterior segment uveitis was comparable to that of patients who participated in an open-label study of the TNFα-inhibitor infliximab, which is considered effective treatment for refractory uveitis. Secukinumab was associated with improvement of visual acuity; reduction in ocular inflammation and the ability to stop corticosteroid therapy. Responses were seen in 11 of 16 patients by week 8, with a mean increase in visual acuity of >2 lines on Early Treatment of Diabetic Retinopathy Study charts and a rapid reduction in vitreous haze that was sustained through follow-up. Preliminary findings from a clinical study of secukinumab used as an adjunct to immunosuppressant therapy in uveitis associated with Behçet’s disease do not support efficacy in uveitis. (Novartis data on file) More data beyond the studies discussed here will be necessary to assess the potential role of secukinumab in this condition.
Ankylosing spondylitis

Safety and efficacy of secukinumab were evaluated in AS in a randomised, double-blind, placebo-controlled phase II study (N=50).51 52 The primary efficacy endpoint was the rate of Assessment of SpondyloArthritis International Society-20 response at week 6. The primary endpoint analysis employed a Bayesian method and included historical data on placebo responses from eight representative trials in AS. Secukinumab was associated with an Assessment of SpondyloArthritis International Society-20 response rate at week 6 of 61% compared with 17% for placebo (p<0.05), with a probability of positive treatment difference of 99.8%. In a MRI substudy, improvements in radiological scores with secukinumab were evident as early as week 6 and were sustained up to week 28. Interim safety analysis showed that the safety profile of secukinumab was consistent with results from other studies, with no early safety signals observed.51 52

Crohn's disease

On the basis of the known role of IL-23 in promoting intestinal inflammation via mediators such as IL-6 and IL-17A,53 a POC study was initiated to assess the efficacy of secukinumab in CD. In the double-blind, phase IIa trial, 59 participants with moderate to severe CD (ie, a score of 220–450 on the CD Activity Index (CDAI)) were randomised (2:1) to secukinumab 10 mg/kg or placebo, administered as an IV infusion on days 1 and 22. Efficacy and safety were assessed through 18 weeks of follow-up, and the primary efficacy endpoint was mean change in CDAI score at week 6. There was no significant difference in mean improvement in CDAI score between the secukinumab-treated group (−29.2 points) and the placebo-treated group (−65.1 points) at week 6 or any other time point. More secukinumab-treated participants (17/39) experienced infection as an adverse event than placebo-treated participants (0/20).54

The negative results of this secukinumab study may be explained by the apparent protective function of IL-17A in the intestine, as observed in an animal model of colitis.55 More research is needed to verify the postulated role of IL-17A in CD pathophysiology.

ASSESSING ANTI-IL-17 MAB THERAPIES: RESULTS AND COMPARISONS

Clinical trials of therapies targeted at the proinflammatory cytokine IL-17A have substantiated mechanistic research on the pathophysiology of autoimmune disorders. Phase II data on secukinumab, ixekizumab, and brodalumab in psoriasis indicate rapid and pronounced effects on measures of disease activity. Early clinical trials in PsA, RA, and AS also support the therapeutic utility of IL-17A inhibition. The results of pivotal phase III trials are needed to draw definitive conclusions regarding efficacy and safety in autoimmune disease. Phase III trials of secukinumab are currently being conducted in patients with moderate to severe plaque psoriasis, including a placebo-controlled trial with a 1-year follow-up (ERASURE), a head-to-head trial comparing secukinumab with etanercept (FIXTURE), a trial comparing a fixed-dose secukinumab regimen with a secukinumab regimen of retreatment after relapse (SCULPTURE), and a trial comparing IV and SC dosing (STATURE). Phase III trials of secukinumab are also ongoing in PsA (FUTURE 1) and RA, including trials comparing secukinumab with placebo (REASURE 1) or abatacept (NURTURE 1) in RA patients who previously experienced inadequate response to TNFi-inhibitor therapy. A phase III study with follow-up of up to 2 years is currently under way in AS (MEASURE-1), and another phase III AS study with follow-up as long as 5 years is planned.56 No phase III trials of brodalumab have been disclosed.56 Phase III trials of ixekizumab are being conducted in moderate to severe plaque psoriasis, including: a 12-week, placebo-controlled trial with a 1-year extension (UNCOVER-1); trials comparing ixekizumab with etanercept (UNCOVER-2 and UNCOVER-3); and a trial in a Japanese population. A phase III trial of ixekizumab compared with adalimumab in the treatment of PsA is planned (SPIRIT-P1).56

A potentially important area of future clinical research will be whether fully human wild-type Fc monoclonal antibodies such as secukinumab58 and brodalumab59 carry less potential for immunogenicity than humanised and hinge-modified antibodies such as ixekizumab.52 In addition, whereas secukinumab and ixekizumab selectively target and neutralise IL-17A, brodalumab binds the IL-17RA chain of the heteromeric IL-17 receptor, which is shared with multiple members of the IL-17 cytokine family and is therefore expected to inhibit the biological activity of IL-17A and IL-17F as well as IL-17C.60 IL-17E (IL-25) and potentially other not yet discovered IL-17 family members that utilise IL-17RA.61 Whether differential targeting by these agents could lead to distinct clinical effects remains to be seen.

Relative to other biologicals, agents that target IL-17A or its receptors have the theoretical potential to exert more targeted effects on the immune system. Therapies that modulate IL-23/12 directly (such as ustekinumab) would be expected to affect Th1 and Th17 differentiation, and TNFα-inhibitors target a pleiotropic cytokine with broad effects on the immune system. Whether this hypothetical advantage for IL-17A inhibitors translates into any clinical benefits will be a question of interest as data from phase III studies becomes available.

CONCLUSIONS

IL-17A plays a critical role in the pathogenesis of a range of autoimmune diseases, including psoriasis, RA, PsA and AS. Secukinumab is one of several antibodies targeting IL-17A signalling that are in clinical development for the treatment of autoimmune diseases. Although all of the agents target IL-17A either directly or indirectly, pharmacological differences exist among them. Secukinumab, an IgG1 mAb, and brodalumab, an IgG2 mAb, are fully human, whereas ixekizumab is a hinge-modified IgG4 humanised mAb. Secukinumab and ixekizumab target a soluble cytokine (IL-17A), whereas brodalumab blocks the IL-17RA chain of the IL-17 receptor on the cell surface. Results from ongoing phase III studies in autoimmune diseases will allow us to better assess whether these differences may result in clinically relevant differences among these agents. Another intriguing question that may be addressed in these trials is whether IL-17A-based therapies as a class exert more targeted effects on the immune system than existing biologicals.

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