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# Interleukin-17 inhibition in psoriatic arthritis

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## ABSTRACT

*Greater understanding of the underlying disease process has led to the development of targeted therapeutic agents and innovative strategies in the treatment of psoriatic arthritis (PsA). This report addresses novel medications targeting the T helper 17 cell pathway, specifically those inhibiting interleukin-17A and its receptor, and discusses their role as effective therapies in the management of PsA.*

## Introduction

Psoriatic arthritis (PsA) is a heterogeneous condition with diverse clinical manifestations that include peripheral and axial arthritis, enthesitis, dactylitis, skin and nail psoriasis, and other manifestations (1). The severity of involvement varies widely, both within domains and among individual patients. Tumour necrosis factor inhibitors (TNFi) can be effective in treating all cardinal features of PsA with the majority of patients achieving a prompt and sustained response. Nevertheless, some patients do not respond to TNFi, and others experience loss of efficacy over time or achieve less of a clinical response than desired (2, 3). Furthermore, some patients experience adverse events with TNFi and cannot tolerate these agents.

One strategy to deal with these inadequate responders or 'TNFi failures' is to change to medications with an alternative mechanism of action. The possibilities include ustekinumab and apremilast, which have been recently approved for treatment of PsA (4, 5), but also interleukin-17 (IL-17) inhibitors, which currently are in advanced stages of clinical trials in PsA. Among the latter group are secukinumab and ixekizumab, which are human and humanised monoclonal antibodies that target IL-17A, respectively, and brodalumab, a human monoclonal antibody that blocks the IL-17A receptor. Herein, we discuss the rationale for using

IL-17 inhibitors in PsA, evidence for their efficacy and safety considerations reported from clinical trials to date, and consider their role in the approach to treatment of PsA.

## Rationale for IL-17 inhibition in PsA

The importance of T helper 17 (Th17) cells and their associated cytokines, including IL-17, IL-22 and IL-23, in the pathogenesis of PsA, among other autoimmune inflammatory conditions, has increasingly been recognised (6). Elevated numbers of Th17 cells have been detected in the circulation of patients with spondyloarthritides, and in the synovial fluid, synovium, and skin psoriasis plaques of patients with PsA (7-9). As a result, anti-cytokine therapies broadly targeting the Th17 pathway (e.g. ustekinumab and IL-17 inhibitors) have been developed, and are showing promise as effective alternatives to TNF inhibition in the management of PsA.

Th17 cells produce a variety of cytokines and other inflammatory mediators, including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F (of which, the most potent driver of chronic inflammation is IL-17A), as well as IL-22, IL-26 and the chemokine CCL20 (10). In inflammatory states, IL-17 is produced predominantly by Th17 cells and elicits an inflammatory response resulting in inflammation in the skin, entheses and synovium (11).

Inflammation of the entheses, or attachments of tendons or ligaments to bone, has been proposed as an etiopathogenic lesion that could explain some of the varied clinical manifestations seen in PsA. The enthesal region has been shown to contain a unique population of resident T cells that, when activated by IL-23, produce an inflammatory response through release of inflammatory mediators including IL-17 and IL-22 (12). This process is driven primarily by IL-17, and is hypothesised to elicit synovitis in the contiguous joint

– a concept described as the “synovio-entheseal complex” (13).

IL-17 works synergistically with TNF- $\alpha$ , and together these cytokines are responsible for cartilage destruction and bone erosion (10). By contrast, IL-22 is believed to result in osteoproliferation, potentially contributing to the characteristic bony proliferation and ankylosis seen in PsA (14). The phenomenon of both processes occurring simultaneously is a radiographic hallmark of PsA. Because they may result from inflammatory cytokines secreted by Th17 cells, targeting this cellular pathway may be an effective way to treat multiple aspects of the disease process in PsA (15).

### Clinical studies on IL-17 inhibition in PsA

#### *Secukinumab*

##### *(anti-IL-17A monoclonal antibody)*

Secukinumab was found to be effective in treating skin psoriasis in two phase 3, randomised placebo-controlled trials (16). In the ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) study (n=738), the proportion of patients who had a reduction of 75% from baseline in the psoriasis area-and-severity index (PASI75) score was attained by 81.6 and 71.6% of patients who received 300 and 150 mg of secukinumab, respectively, by week 12, compared with 4.5% of control patients. The FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) study (n=1,306) also documented significant improvement in patients who received 300 and 150 mg of secukinumab – PASI75 scores at week 12 were 77.1 and 67.0%, respectively, compared with 4.9% of control patients.

Two phase 3 randomised, placebo-controlled trials of secukinumab in PsA have been conducted. In FUTURE 1, 606 patients were randomised to receive varying doses of secukinumab (with intravenous loading, followed by either 150 or 75 mg subcutaneously) vs. placebo (17, 18). The primary endpoint was American College of Rheumatology 20 (ACR20) response at week 24, and was met by 50.0 and 50.5% of

patients who received 150 and 75 mg of secukinumab, versus 17.3% in the control arm ( $p<0.001$ ). Secondary endpoints included resolution of enthesitis, dactylitis and skin disease, inhibition of radiographic progression, and improvements in function and quality of life; these endpoints also differed statistically significantly in the active treatment versus control groups. This study population included 35% of patients who had prior TNFi exposure; secukinumab was superior in both groups over control, although slightly better outcomes were observed in TNF-naïve patients. In FUTURE 2, 397 patients were randomised to receive secukinumab, 300 or 150 mg subcutaneously, or placebo at standardised intervals (19). The primary endpoint was ACR20 response at week 24 and was met by 54.0 and 51.0% of patients who received 300 and 150 mg of secukinumab, respectively, versus 15.3% of control patients ( $p<0.0001$ ). Secondary endpoints included improvements in multiple domains of PsA including enthesitis, dactylitis, skin psoriasis, and quality of life, all of which were significantly greater in the active treatment versus control group. Efficacy in both TNF-naïve patients and the 35% of patients with prior TNF exposure was superior to that seen in control patients, again with a slightly lesser response in TNF-exposed patients.

#### *Ixekizumab*

##### *(anti-IL-17A monoclonal antibody)*

Ixekizumab also has documented efficacy in treatment of skin psoriasis. A phase 2 study of 142 patients documented a rapid and significant response, as 76.7, 82.8 and 82.1% met PASI75 responses after treatment with 25, 75, or 150 mg, respectively, compared with 7.7% in control patients (20). Ongoing studies of ixekizumab in PsA, include a phase 3, randomised, double-blind, placebo-controlled trial, titled SPIRIT-P1, in which patients with active psoriasis were randomised to receive ixekizumab (160 mg starting dose, followed by 80 mg administered subcutaneously either every 2 or 4 weeks) versus control patients, the primary outcome measure being ACR20 response at 24 weeks (clinicaltrials.gov – NCT02349295).

It was reported publicly in April 2015 that the primary outcome was met with ixekizumab demonstrating significant improvements compared with the control group (21).

#### *Brodalumab*

##### *(anti-IL-17 receptor monoclonal antibody)*

Brodalumab blocks the IL-17A receptor, and therefore, it has the capacity to block IL-17 signalling more broadly (*i.e.* it can interfere with other members of the IL-17 family that also utilise this receptor). In a phase 2 study of 198 patients with plaque psoriasis treated with brodalumab, significant efficacy in treating skin lesions was seen (22). At week 12, PASI75 responses were seen in 77 and 82% of patients who received 140 and 210 mg of brodalumab, respectively, compared with 16% of control patients. As with anti-IL-17A monoclonal antibodies, the rapid and significant skin response seen with brodalumab can almost serve as a ‘positive control’ of drug efficacy in clinical trials in PsA.

A phase 2 study of brodalumab in 168 patients with PsA indicated that this medication also improved outcomes in psoriatic arthritis (23). The primary endpoint was ACR20 response and was met by 37 and 39% of patients receiving 140 and 280 mg of brodalumab, respectively, compared with 18% in those control patients. These results improved at week 24 with 51 and 64% of patients, respectively, meeting the primary outcome, and the improvements were sustained at 52 weeks. Patients who switched from placebo to brodalumab also benefited, improving from an 18% ACR20 response at week 12 to 44% at week 24. Improvement was seen in many other clinical domains and will be studied further. Importantly, efficacy was similar in patients who had received prior biologic therapy, indicating that brodalumab could be a potential alternative in TNF incomplete responders. Whether this result will be reproduced in subsequent studies remains to be determined.

### Safety profile of IL-17 inhibitors in PsA

In addition to its role in autoimmune disease, the fundamental function of

IL-17A is in host defense, particularly with respect to extracellular bacterial and fungal pathogens attacking mucosal sites (24). As a result, inhibition of IL-17A potentially increases the risk of infections. Indeed, genetic defects affecting the IL-17 pathway (e.g. STAT3 deficiency) are associated with chronic mucocutaneous infections caused by *Candida albicans* (25). However, IL-17 inhibitors appear to have been well tolerated in clinical trials reported to date, with infection rates being only slightly higher than those observed in control patients. The most commonly reported adverse events include nasopharyngitis, upper respiratory tract infection, headache, diarrhoea, and cytopenia (mild neutropenia). Significant adverse events (SAE) have also been very infrequent, with rates only slightly higher than those reported in the control arms.

In a pooled safety analysis of two phase 3, randomised, placebo-controlled trials (FUTURE 1 and FUTURE 2), the incidence of *Candida* infections (0.7 and 1.6%, respectively), neutropenia (1.3 and 1.7%, respectively), and malignancy (0.3 and 0.5%, respectively) was low with secukinumab (26). While results thus far are promising, further trials and studies of longer duration are needed to adequately assess the safety profile of IL-17 inhibitors in PsA.

#### **Inhibition of IL-12/23 with ustekinumab in PsA**

Ustekinumab is a monoclonal antibody directed against the common p40 subunit of IL-12 and IL-23 that has been approved for use in the treatment of skin psoriasis and PsA in many countries worldwide. In addition to TNF- $\alpha$  and IL-17, IL-12 and IL-23 also appear to be involved in the immunopathogenesis of psoriasis and PsA (27). These cytokines are secreted by dendritic cells and help determine the differentiation of naïve T cells, in the case of IL-23 into Th17 cells. Activation of Th17 cells via IL-23 results in increased production of IL-17, which subsequently elicits an inflammatory response in the skin, entheses, and synovium leading to the characteristic manifestations of PsA. Increased expression of IL-23 and

the p19 subunit of IL-23 have been detected in psoriatic skin lesions and synovium, respectively (28, 29).

Data from phase 3 clinical trials (PSUMMIT 1 and 2) have shown significant improvement in psoriatic skin disease, peripheral arthritis, enthesitis, dactylitis, and physical function with ustekinumab therapy. PSUMMIT 1 was a two-year randomised, placebo-controlled trial that evaluated patients (n=615) with active PsA who were TNFi naïve (30). Patients received ustekinumab (45 mg or 90 mg) or placebo at weeks 0 and 4, and every 12 weeks thereafter. The primary endpoint was ACR20 response at week 24 and was achieved by 42.4 and 49.5% of patients treated with ustekinumab (45 and 90 mg, respectively) compared with 22.8% in the control arm. Improvements in enthesitis, dactylitis, PASI75 response, and function were also greater in ustekinumab-treated patients compared with the control group.

PSUMMIT 2 assessed the efficacy and safety of ustekinumab in 312 patients with active PsA despite prior treatment with conventional agents and/or TNFi (31). This randomised, double-blind, placebo-controlled trial again looked at ACR20 response at week 24 as the primary endpoint, with secondary endpoints including assessment of physical function and skin response. More patients treated with ustekinumab (either 45 mg or 90 mg at weeks 0, 4, and every 12 weeks thereafter) achieved ACR20 response at week 24 than in the control arm (43.8 vs. 20.2%, respectively;  $p < 0.001$ ). There were also significant treatment differences observed between the ustekinumab-treated and control patients with respect to psoriatic skin disease, enthesitis, dactylitis, and physical function. It is noteworthy that of the patients included in this study, 180 had prior TNFi exposure, with a majority having received  $\geq 2$  TNFi previously. These patients also demonstrated improvements in ACR20 (35.6%) and PASI75 (47.1%) responses, although the values were slightly lower than in TNFi-naïve patients (54.4 and 60.5%, respectively).

The improvements in PsA signs and symptoms with ustekinumab were sus-

tained at week 52 in both biologic-naïve and TNFi-exposed patients (30, 31). In addition, ustekinumab has demonstrated efficacy in decreasing radiographic progression of joint damage in both groups of patients (32). There is long-term safety data for ustekinumab in the treatment of skin psoriasis (33). Results from PSUMMIT 1 and 2 showed adverse events were similar across treatment groups in these studies with infrequent serious infection and injection-site reactions (30-32). Overall, this medication appears to be a good alternative in patients who cannot tolerate or have incomplete response to TNFi.

#### **Research agenda**

##### *Is there an optimal patient for IL-17 inhibition?*

The rapid and substantial improvement of psoriasis with IL-17 inhibition may favour the use of these medications in patients who have prominent skin lesions. Accumulating data also indicate that these agents also are effective in treating peripheral arthritis in PsA, while the same does not hold true in rheumatoid arthritis (RA) – highlighting different pathogenic mechanisms of these two diseases (34, 35). Axial involvement in PsA has not been specifically assessed to date, although there is evidence for efficacy of secukinumab to improve signs and symptoms of ankylosing spondylitis (36).

Two patient populations seem less ideally suited for IL-17 inhibition: patients with inflammatory uveitis and those with inflammatory bowel disease (IBD) or nonspecific colitis. Non-infectious uveitis occurs in approximately 7% of patients with PsA (37). Secukinumab has been studied in the treatment of non-infectious uveitis in 3 trials, one which focused on Behçet's disease and two which focused on patients with inflammatory uveitis excluding those with Behçet's (38). The primary outcome was not met in any of the studies, i.e. no difference was observed in uveitis recurrence rates between patients treated with secukinumab *versus* placebo.

Pilot studies of IL-17 inhibitor use for treatment of IBD will likely preclude further study of these agents in this dis-

ease, in part due to its lack of benefit, but also due to its potential to cause disease flare (39). The latter may be a noteworthy consideration in PsA patients in whom gut inflammation, often subclinical, is an extra-articular manifestation reported in a small, but not insignificant proportion of patients. While ongoing vigilance for potential worsening of colitis will be required, a pooled safety analysis of the FUTURE 1 and 2 trials found the incidence of IBD/Crohn's disease to be low with secukinumab (in FUTURE 1, the rate was 0.3% with a similar value reported among patients treated with placebo) (26).

#### Where do IL-17 inhibitors fit into the treatment paradigm?

As noted previously, growing evidence is available from clinical trials that IL-17 inhibition can be effective in treating cardinal manifestations of PsA. No head-to-head comparison with other biologic therapies has been performed. Efficacy of IL-17 inhibitors has been documented in treating patients who had inadequate response to TNFi. As few alternative choices are available at this time, IL-17 inhibitors are a promising option in this patient population. Further studies are required to determine the most appropriate place in the treatment paradigm.

#### Is there any role of combination therapy with IL-17 inhibitors?

In RA, the combination of methotrexate (MTX) and anti-TNF therapy has demonstrated synergistic efficacy in clinical trials (40). In contrast, whether PsA patients might have improved outcomes with concomitant use of MTX with TNFi has not been studied systematically. To date, clinical trials in PsA involving IL-17 inhibition have allowed the concomitant use of stable doses of MTX, but no comparison has been made between those taking and not taking MTX. Combination therapy with other DMARDs, such as apremilast, has not yet been studied as a potentially effective therapeutic regimen. Most therapies in PsA are based on inhibition of a single cytokine (e.g. TNF- $\alpha$ ). Recently, the effects of combined inhibition of TNF- $\alpha$  and IL-17

on suppression of inflammation in RA were investigated in a mouse model (41). The effects of 'combined blockade' were more effective than 'single blockade' in preventing inflammation and also reducing damage of cartilage and bone. Thus, bispecific antibodies targeting combinations of cytokines or inhibitors may be more effective than single cytokine blockade and may help overcome some of the challenges faced in patients with poor response to therapy. Whether these results will prove fruitful in human trials and can then be extrapolated to PsA remains unknown. One caveat of synergistic suppression is the potential for increased risk of infection, as was noted in mouse models of RA with combined inhibition of TNF- $\alpha$  and IL-1 (42).

#### Summary

Clinical evidence reviewed here suggests targeting the Th17 cellular pathway through IL-17A inhibition is an effective alternative to TNF- $\alpha$  inhibition in the treatment of PsA. These therapies have demonstrated improvement, not only in skin psoriasis and peripheral arthritis, but accumulating evidence also suggests efficacy in multiple other domains of PsA. Thus, IL-17 inhibition appears to be a promising and effective strategy for treating PsA.

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