ABSTRACT
The cytokines interleukin (IL)-12 and interleukin (IL)-23 have been implicated variously in the pathogenesis of psoriasis and psoriatic arthritis (PsA). By corollary, the IL-12/23 inhibitor, Ustekinumab has been developed as an approved therapeutic for the skin and musculoskeletal syndrome of psoriasis / PsA. This review describes briefly the role of IL-12 and IL-23 in the pathophysiology of psoriatic arthritis and evaluates trial data that support its clinical use in psoriasis and different manifestations of psoriatic arthritis. The next steps towards targeting this pathway also are discussed.

Introduction
A major advance over the last decade has been recognition that the IL-23/IL-17 cytokine axis plays a major role in a variety of human autoimmune diseases. The core paradigm proposes that T-helper-17 (Th17) effector cells play an integral role in the pathophysiology via the elaboration of interleukin 17A (IL-17A) which acts on multiple cell types, including cells of the innate immune system, fibroblasts, enteroctyes and keratinocytes. Th17 cells also release a variety of other cytokines of inflammatory potential including TNF, IL-17F and IL-22, together with a variety of chemokines that can further serve to amplify the diathesis, often acting in synergy with IL-17A. This axis has a primary role in host defence at mucosal sites, e.g. against fungal and gram positive infections, and in maintenance of immune homeostatic regulation in the gastrointestinal tract (2, 3). In psoriasis and PsA there is now evidence of dysregulation of Th17 cells, associated with overproduction of IL-17A (1). Accordingly, substantial interest has emerged to develop therapeutic agents which target this pathway directly, via IL-17 inhibition, or upstream via blockade of IL-23. Whether a naïve CD4 T-cell differentiates into a Th1, Th2 or Th17 phenotype is determined by cytokines produced largely by cells of the innate immune system, particularly dendritic cells. Early Th17 development is supported by IL-1, IL-6, TGFβ and IL-21. Many murine and human studies have demonstrated clearly that IL-23, which is composed of the two subunits p19 and p40 (2, 3) plays a critical role by driving the expansion and functional maintenance of Th17 development. The p40 subunit of IL-23 is shared with IL-12 (which forms a heterodimer with p35), but rather than inducing naïve CD4 T-cell differentiation into the Th17 cell lineage, IL-12 induces Th1 differentiation (3). Since Th1 and Th17 cells can oppose each other in terms of effector function and cell survival, the biology of IL-12 and IL-23 should not be considered common or overlapping despite their structural similarities.

A role for IL-12 and IL-23 in the pathophysiology of psoriatic arthritis has been suggested in multiple studies. Gene association studies link PsA with variants of the IL-12β, IL-23A and the IL-23 receptor (4), there is overexpression of IL12p40 and IL23 (p19 and p40 subunits) in psoriatic plaques (5-7) and IL-23 is expressed in synovia of inflamed joints (8). Furthermore, blocking the pathway can successfully treat the disease, as will be discussed below. However it is now evident that it is probably IL-23 that drives the critical effector pathways in the psoriasis spectrum rather than IL-12 – this has significant implications for the next step of therapeutic evolution in treatment of these diseases.

Targeting the IL-12 and IL-23 pathway to treat psoriasis
Ustekinumab is a human monoclonal antibody which binds to the p40 subunit shared by IL-12 and IL-23, pre-
venting binding to the IL12Rβ1 cell surface receptor and thereby inhibits the activity of both cytokines. It was first developed to treat moderate-to-severe plaque psoriasis and a recent meta-analysis found that the risk ratio (RR) for achieving Psoriasis Area and Severity Index improvement by 75% (PASI75) at week 12 was 18.28 (CI 12.76–26.17 p<0.001) for ustekinumab 45 mg compared to placebo and 20.21 (CI 13.85–29.49 p<0.001) for ustekinumab 90 mg compared to placebo (9). No significant difference was found between the two ustekinumab groups. Whereas this meta-analysis did not consider improvements beyond week 12, the phase 3 studies PHOENIX 1 and 2 both demonstrated improvement over longer periods, now sustained through several years, if the drug is tolerated. Maximum responses were observed at about week 24 and 20 respectively, with 76% responders in the ustekinumab 45 mg group and 85% in the ustekinumab 90 mg group observed in PHOENIX 1 (10). The corresponding PASI75 response rates in PHOENIX 2 were 74.9% and 83.5% (11). The response was generally maintained in patients continuing treatment to completion of each study, whereas deterioration was reported in patients who were randomised to withdrawal of treatment.

Ustekinumab also performed well compared to the tumour necrosis factor α (TNF-α) inhibitor etanercept, as demonstrated in the ACCEPt study. The rates of PASI75 at 12 weeks were 56.8%, 63.5% and 73.8% in the etanercept 50 mg, ustekinumab 45 mg and ustekinumab 90 mg groups respectively (12). The proportion of patients who achieved PASI90 and had cleared ≥5/66 swollen and ≥5/68 tender joints from screening and baseline, serum C-reactive protein ≥3mg/L, and active or a documented history of plaque psoriasis. 615 patients were enrolled in PSUMMIT 1 and 312 into PSUMMIT 2. Patients were randomised 1:1:1 to control, ustekinumab 45 mg or ustekinumab 90 mg given at week 0, week 4 and every 12 weeks thereafter. Randomisation was stratified by methotrexate use and weight. Patients in the control groups were crossed over to active treatment at either week 16 or week 24 depending on response.

**Ustekinumab on peripheral synovial joint inflammation**
Evidence of efficacy compared to placebo for ustekinumab was noted by weeks 4–8 in PSUMMIT 1 (17). The primary end point of both studies was improvement of 20% or greater in American College of Rheumatology criteria (ACR20) at week 24; this was achieved in 22.8%, 42.4% and 49.5% in the control, ustekinumab 45 mg and ustekinumab 90 mg groups respectively in PSUMMIT 1 (17). The corresponding response rates were slightly lower at 20.2%, 42.4 and 43.8% in PSUMMIT 2, reflecting the presence of prior TNFi recipients (18). Significantly more patients in the ustekinumab groups achieved ACR70 in both studies and ACR90 in PSUMMIT 1. ACR20 improvement was maintained throughout the 52 week follow up period in both studies. Improvement in joint inflammation was also evaluated using the 28 joint count disease activity score using CRP (DAS28-CRP) and the European League against Rheumatism (EULAR) response criteria. At week 52 of PSUMMIT 1, approximately 60% of patients in all groups had achieved ACR20 and good or moderate DAS28 CRP response as defined by EULAR, with remission rates of 30.8% in the combined ustekinumab group and 29.3% in patients who had been crossed over from control to ustekinumab 45 mg (17). In PSUMMIT 2, 19.6% of ustekinumab treated patients were in remission (18). Approximately half of patients in PSUMMIT1 took methotrexate. Although no statistical analysis was performed, the ASR20 response rates were numerically higher in patients not taking methotrexate.

**Enthesitis, spondyloarthropathy and dactylitis**
PsA is a heterogenous disease which...
can manifest as dactylitis, enthesitis and spondyloarthritides. The effect of treatment on these disease compartments was evaluated in secondary analyses in both PSUMMIT trials. Of those patients with dactylitis at day 0 in PSUMMIT 1, 76.1% in the control group, 56.6% in the ustekinumab 45mg group and 55.8% in the ustekinumab 90mg group had residual dactylitis at week 24 (17). A numerical difference in the proportion of patients with residual dactylitis was seen in PSUMMIT 2 (75.8% placebo, 65.2% ustekinumab 45mg and 57.9% ustekinumab 90mg), but this was not statistically significant (18). There was a significant improvement in patients with residual enthesitis in both studies and in PSUMMIT 1; the Psoriatic arthritis-modified Maastricht ankylosing spondylitis enthesitis (MASES) score improved significantly, with a median change of approximately 50% at week 24 (17). Significantly more patients achieved a 20% response in the Bath Ankylosing Spondylitis activity index (BASDAI20) in PSUMMIT 1 with response rates of 26.2%, 49% and 58.3% in the control, ustekinumab 45mg and ustekinumab 90mg groups respectively. Post-hoc sub-analysis of the 186 patients in PSUMMIT 1 with spondylitis with peripheral joint involvement at recruitment showed that improvements in MASES index and dactylitis scores were maintained at week 100 (19).

Structural damage
The IL-23-Th17-IL-17 pathway has been linked to osteoclast activation and by inference the potential for bone destruction (20). Ustekinumab inhibits radiographic progression in PsA (21). Radiographic evaluations of the hands and feet of subjects enrolled in the PSUMMIT trials were assessed using the PsA-modified van der Heijde-Sharp (vDH-S) score that calculates erosions and joint space narrowing scores. At week 24, significantly more patients in the combined ustekinumab treated group compared to control demonstrated no radiographic progression (91.7% vs. 83.8%, p=0.005). The inhibition of radiographic damage was sustained to week 52. A decrease in progression was also seen in patients who originally were in the placebo group and crossed over to active therapies. The proportion of patients with ‘pencil-and-cup’ or gross osteolysis deformities remained low and stable throughout the study in all groups.

The adverse events profile in the PSUMMIT trials was similar to previous trials in psoriasis (17, 18) and subgroup analysis of trials in psoriasis did not find any significant difference (22). Aggregation of Phase II and Phase III studies reported 348 adverse events per 100 patient-years in patients treated with placebo compared to 375 in patients treated with ustekinumab (23). There was no significant difference in serious adverse events rates per 100 patient years in the ustekinumab groups compared to the placebo group.

Summary and the next steps in treatment
There are several lines of evidence for a role of IL-23 in the pathogenesis of PsA. Suggestive pre-clinical biology is strongly supported by the clinical efficacy of ustekinumab in treating PsA. However, responses are not universal and improvement in skin psoriasis does not necessarily correspond to significant improvements in joint symptoms. In general, skin responses are more robust than those seen in articular disease. Other manifestations of disease, including dactylitis, enthesitis and spondyloarthritides improve with treatment but thus far, have been evaluated only in secondary analyses.

The observation in animal models that IL-23 deficient mice are protected from disease but IL-12 deficient mice develop more severe joint inflammation, suggests a potential protective role of IL-12 (24.) Consequently, ‘pure’ IL-23 inhibitors may have a theoretical advantage over ustekinumab. The small studies in psoriasis to date have shown promise, but studies of their use in PsA are awaited – several clinical trials are ongoing. An alternative approach is to target the IL-23/IL-17 pathway down-stream. Ustekinumab inhibits IL-23/IL-17 pathway down-stream. An alternative approach is to target the IL-12 and IL-23 inhibition in PsA / H.J. Johnsson & I.B. McInnes

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