Nature Reviews Rheumatology **10**, 125 (2014); published online 18 February 2014; doi:10.1038/nrrheum.2014.24

THERAPY

Ustekinumab after anti-TNF failure: a step closer to the PSUMMIT of psoriatic arthritis therapy?

The results through 60 weeks of the PSUMMIT 2 trial, now published in *Annals of the Rheumatic Diseases,* reveal that patients with active psoriatic arthritis (PsA), including those previously treated with one or more TNF inhibitors, demonstrated considerable improvements in the signs and symptoms of the disease following treatment with the IL-12/IL-23 inhibitor ustekinumab.

A monoclonal antibody that targets the p40 subunit shared by IL-12 and IL-23, ustekinumab (Stelara®; Janssen Biotech, Inc.; Horsham, PA, USA) was first approved for use in psoriasis and has shown clinical benefit for PsA in a previous phase III trial (PSUMMIT 1). "While the efficacy of ustekinumab was demonstrated in the PSUMMIT 1 trial as well, that trial did not include anti-TNF-treated patients," explains Dafna Gladman (University of Toronto, Canada), who was not an author on the studies.

In the phase III, multicentre, placebo-controlled PSUMMIT 2 trial, 312 adults with active PsA despite treatment with DMARDs, NSAIDs and/or anti-TNF therapy (132 were anti-TNF-naive, 180 had received prior anti-TNF therapy) were randomly allocated to receive subcutaneous ustekinumab 45 mg or 90 mg at week 0, week 4 and every 12 weeks thereafter, or placebo at week 0, week 4 and week 16 followed by crossover to ustekinumab 45 mg at week 24, week 28 and week 40.

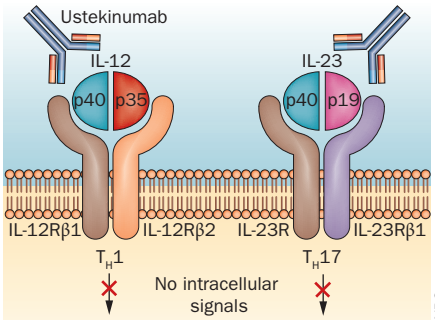
At week 16, patients who demonstrated <5% improvement in tender and swollen joint counts entered a blinded 'early escape' phase, whereby those receiving placebo were switched to ustekinumab 45 mg, those receiving ustekinumab 45 mg had the dose increased to 90 mg, and those receiving ustekinumab 90 mg continued on that dose. "This is the design that has been used for many PsA trials, where patients are randomized but there is an escape at 16 weeks," says Gladman. "Since we now have drugs that are effective for PsA, it would be unethical to continue placebo for 6 months."

Of note, concomitant therapy with methotrexate, NSAIDs and oral corticosteroids (≤10 mg prednisone per day) was permitted at stable doses.

The primary endpoint of at least 20% improvement according to ACR criteria (ACR20) at 24 weeks was achieved by a significantly higher proportion of ustekinumab-treated patients than those who received placebo (43.7% and 43.8% for ustekinumab 45 mg and 90 mg, respectively, versus 20.2% for placebo). Clinical response to ustekinumab was maintained through 52 weeks, with peak efficacy apparent at 24–28 weeks.

Significant differences between the treatment and placebo groups were also observed for several secondary endpoints measured at 24 weeks, including improvements in Health Assessment Questionnaire-Disability Index (HAQ-DI), ACR50, ACR70 and ≥75% improvement in Psoriasis Area and Severity Index (PASI75) response rates. These benefits of ustekinumab treatment were also sustained through week 52.

Ustekinumab seemed to be effective regardless of methotrexate use at baseline or body weight (≤100 kg or >100 kg). Notably, the drug was effective in patients with prior exposure to TNF inhibitors, more than 70% of whom had discontinued that therapy because of lack of efficacy or intolerance. As Gladman highlights, "This is important since not all patients respond to anti-TNF agents and we need agents that work through different mechanisms." Among the 180 patients with prior exposure to anti-TNF therapy, 35.6% of those in the combined ustekinumab groups versus 14.5% in the placebo group achieved an ACR20 response at week 24. PASI75 response rates and improvements in HAQ-DI were also considerably greater in the treatment groups compared with the placebo group.



Most of those who had received prior anti-TNF therapy had been treated with two or more of these agents, most commonly etanercept, adalimumab and infliximab. Response rates to ustekinumab at 1 year seemed to be lower in patients previously treated with more than one anti-TNF agent than in those treated with only one, although these comparisons were limited by the small numbers of patients in each category.

With respect to safety, adverse events (AEs) and serious AEs were similar in the ustekinumab and placebo groups through week 16, and no unexpected AEs were observed through week 60.

One limitation of the PSUMMIT 2 results presented in this publication is that they do not include data on whether ustekinumab inhibits joint destruction in patients with PsA. "We need to know whether the drug prevents radiologic progression so that we can put it in proper perspective," Gladman points out. An integrated analysis of the radiographic findings from both the PSUMMIT 1 and PSUMMIT 2 trials is expected in a forthcoming publication.

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Original article Ritchlin, C. *et al.* Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2013-204655