

# Ustekinumab: new option for moderate-to-severe psoriasis

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## KEY POINTS

- ustekinumab (Stelara) is a humanised monoclonal antibody that binds to interleukins 12 and 23
- it is licensed for the treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, have a contraindication to or are intolerant of other systemic therapies
- the recommended dose is 45mg by subcutaneous injection at 0 and 4 weeks, then every 12 weeks; a dose of 90mg is needed for patients weighing over 100kg
- is available as a 45mg solution for injection; 1 vial = £2147
- 2 large placebo-controlled trials have shown that ustekinumab achieves substantial improvement in psoriasis severity in most patients, and improves quality of life
- improvement is evident within 2-4 weeks and is sustained during treatment
- clinical trials of up to 76 weeks' duration have not demonstrated an increased risk of serious adverse reactions; the risk of infection is slightly increased compared with placebo
- other currently licensed biologics target TNF-alpha – ustekinumab offers an alternative, and is the treatment of choice where other systemic therapies are unsuitable or have failed



**Ustekinumab (Stelara), a novel biologic for the treatment of moderate-to-severe plaque psoriasis, targets interleukins rather than TNF-alpha. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects and Dr Downs discusses its place in psoriasis treatment.**

Guidance from the British Association of Dermatologists (BAD) states that most cases of psoriasis are mild and can be managed with topical therapies in primary care.<sup>1</sup>

The BAD estimates that 20-30 per cent of patients with psoriasis have severe disease<sup>2</sup> and may benefit from PUVA and/or systemic therapies such as methotrexate, ciclosporin, mycophenolate mofetil (unlicensed), oral retinoids and azathioprine (unlicensed).<sup>1</sup>

If these options are unsuccessful, contraindicated or not

tolerated, treatment with biological therapy may be indicated.

Current National Institute for Health and Clinical Excellence (NICE) guidance recommends adalimumab (Humira)<sup>3</sup> and etanercept (Enbrel)<sup>4</sup> as options for severe psoriasis and infliximab (Remicade)<sup>5</sup> as an option for very severe psoriasis; the value of continuing treatment should be considered after 16, 12 and 10 weeks respectively. Marketing authorisation for efalizumab was recently suspended following reports of progressive multifocal leucoencephalopathy.<sup>6</sup>

## The technology

Ustekinumab (Stelara) is a humanised monoclonal IgG antibody that binds to the cytokines interleukin (IL) 12 and 23.

These cytokines are secreted by activated antigen-presenting cells and play a role in activating natural killer cells and the differentiation and activation of CD4+ T cells. Abnormal regulation of IL 12 and IL 23 is associated with immune disorders including psoriasis.

By blocking these cytokines from binding with their receptor, ustekinumab may interrupt

signalling and cytokine pathways that contribute to psoriasis.

Ustekinumab is licensed for the treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to or are intolerant of other systemic therapies including ciclosporin, methotrexate and PUVA. The recommended dose is 45mg by subcutaneous injection repeated after four weeks and then every 12 weeks; the dose for patients weighing over 100kg is 90mg.

NICE recommends ustekinumab as a treatment option, and that treatment should be evaluated after 16 weeks and discontinued if there has not been an adequate response (75 per cent reduction in the PASI score, or a 50 per cent reduction and a 5-point reduction in the DLQI score).<sup>7</sup>

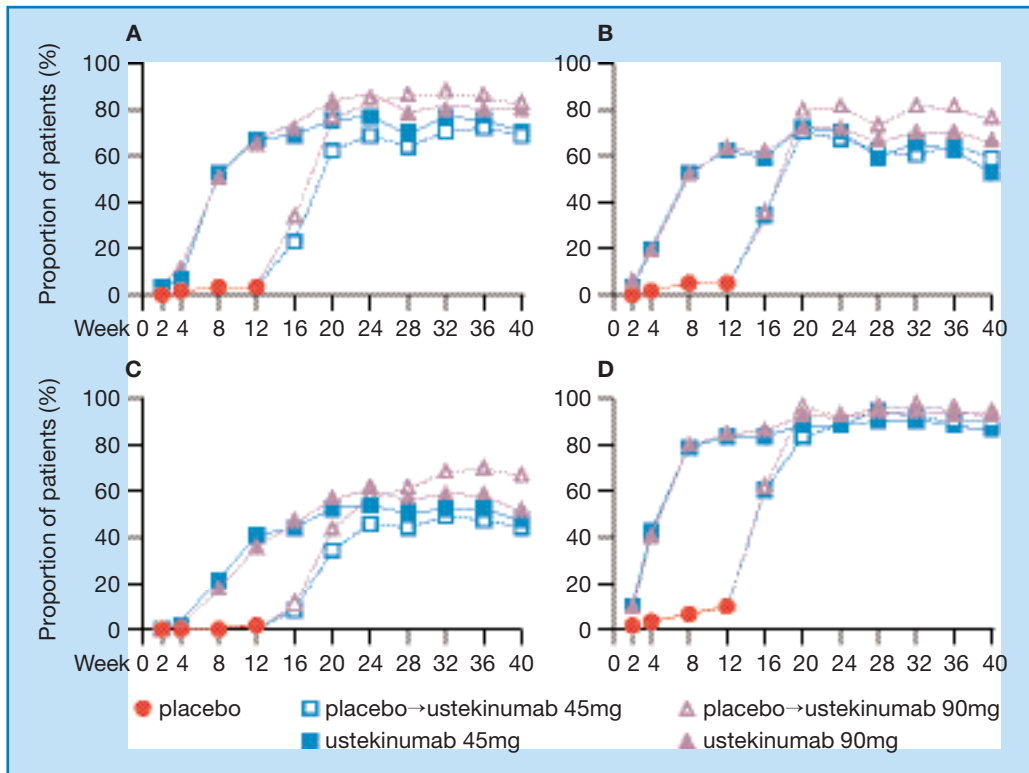
### Clinical trials

Two randomised double-blind trials, PHOENIX 1 (n=766)<sup>8</sup> and 2 (n=1230),<sup>9</sup> provide the key efficacy data for ustekinumab. Both included adults with severe plaque psoriasis (mean Psoriasis Area and Severity Index, PASI, score 20; mean 25-27 per cent of body surface area involved) of at least six months' duration who were candidates for phototherapy or systemic therapy.

There was no requirement for previous treatment so not all participants met the licensed indication. The primary end-point was the proportion of patients achieving a 75 per cent improvement in PASI score (PASI 75) after 12 weeks.

### PHOENIX 1

PHOENIX 1 was a 76-week trial. Patients were randomised to ustekinumab 45 or 90mg at weeks 0 and 4, then every 12 weeks, or placebo at weeks 0 and 4 then randomised again to ustekinumab 45 or 90mg every 12 weeks.



**Figure 1.** Clinical response over 40 weeks in PHOENIX 1;<sup>8</sup> A: PASI 75, B: physician's global assessment of cleared or minimal psoriasis, C: PASI 90, D: PASI 50

Weeks 40-76 constituted a controlled withdrawal trial, in which patients initially randomised to ustekinumab and who had a long-term response (at least 75 per cent improvement from baseline) were once more randomised to continue with ustekinumab or switch to placebo.

About half of patients in this trial had previously been treated with a biological agent, half had received a conventional systemic agent and approximately two-thirds had received phototherapy.

At week 12, PASI 75 rates were 3.1 per cent with placebo, and 67 and 66 per cent respectively with ustekinumab 45 and 90mg. The differences between ustekinumab and placebo were statistically significant by week 2 for PASI 50 and by week 4 for PASI 75, with maximum efficacy evident by week 24. Clearance of psoriasis was achieved in 13 and 11 per cent of patients respectively

with ustekinumab and none with placebo.

By week 28, PASI 75 rates were similar in those continuously treated with ustekinumab (71 and 79 per cent) and those switched from placebo after 12 weeks (66 and 85 per cent). These improvements were maintained until week 40 and were matched by PASI 50 and 90 scores and clinicians' global assessments (see Figure 1). Ustekinumab also improved dermatology-related quality-of-life scores.

The median PASI 75 response did not change in patients who continued ustekinumab to 76 weeks. In those who discontinued treatment, the PASI response began to decrease after week 44; the median time to loss of PASI 75 was 15 weeks but there was no evidence of rebound psoriasis. Some patients started treatment with ustekinumab again, of whom 86 per cent

achieved a PASI 75 response within 12 weeks.

### PHOENIX 2

The first 12 weeks of PHOENIX 2 were the same as for PHOENIX 1. Those assigned to placebo were then randomised again to ustekinumab 45 or 90mg every 12 weeks for 52 weeks. Patients originally assigned to ustekinumab but who achieved only a partial response (PASI  $\geq 50$  -  $< 75$ ) by week 28 were then randomised to the same dose administered every eight (unlicensed) or 12 weeks.

In this trial, about 38 per cent of patients had previously received a biological agent, 56 per cent had received a conventional systemic agent and about two-thirds had received phototherapy.

After 12 weeks, PASI 75 rates were 3.7 per cent with placebo and 68 and 76 per cent with ustekinumab 45 and 90mg respectively. Improvement was again evident by week 2, with a maximum effect by week 20. Clearance occurred in 18 per cent of patients treated with ustekinumab and none with placebo. These improvements were maintained until 52 weeks and were matched by gains in physicians' global assessments and patient-reported quality of life.

At week 28, 23 per cent of patients treated with the lower dose of ustekinumab and 16 per cent of

those at the higher dose were partial responders. Compared with responders they tended to be heavier, have more severe disease and a higher prevalence of psoriatic arthritis, and were more likely to have failed previous systemic or biological therapy. They also had lower blood levels of ustekinumab and a higher prevalence of neutralising antibodies. The eight-weekly dose schedule increased PASI 75 rates with 90mg (69 *vs* 33 per cent) but not 45mg ustekinumab.

### Adverse effects

In placebo-controlled studies, the rate of infections with ustekinumab was 1.39 per patient-year compared with 1.21 with placebo; there was no increase in the rate of malignancies.<sup>10</sup>

The most frequent adverse events reported in PHOENIX 1 and 2 were upper respiratory tract infection, nasopharyngitis, arthralgia, headache, cough and injection-site reaction. These were not clearly more common than with placebo, or after continuous ustekinumab treatment compared with switching from placebo. Arthralgia, cough and headache were more frequent with eight-weekly than 12-weekly administration.<sup>4</sup>

Serious adverse events and events leading to discontinuation were also similar for ustekinumab and placebo.

## Place in therapy

Psoriasis is an incurable chronic skin condition affecting 1 in 50 individuals; up to 20 per cent are reported to be severely affected. Many patients with psoriasis hate the way they look and it has a significant negative impact on their quality of life.<sup>1</sup>

Ustekinumab is a recently licensed treatment for moderate-

to-severe psoriasis in adults who have failed to respond to, are intolerant of, or contraindicated to other systemic therapies. It is a humanised monoclonal antibody targeting two key interleukins, IL12 and IL23, whose overactivity appears to play an important role in psoriasis development.

All other currently licensed biologics target TNF-alpha; ustekinumab offers an alternative, which

## References

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is important because psoriasis is not a straight-forward disease. Its severity can wax and wane, it can become resistant to any treatment and patients can develop side-effects to many of the current alternative treatment options. TNF-alpha antagonists have allowed the effective management of previously untreatable moderate-to-severe psoriasis.

In the comparative ACCEPT

trial (not published), ustekinumab demonstrated significantly superior efficacy to etanercept, the most prescribed anti-TNF biologic in the UK.<sup>2</sup>

Ustekinumab's efficacy has been shown in PHOENIX I and II trials.<sup>3,4</sup> PASI 75 scores were achieved in 67 per cent of participants at 12 weeks and in 71 per cent by 28 weeks (45mg dosage); at 90mg dosage this latter figure rose to 85 per cent.

Efficacy is sustained with no deterioration of psoriasis after 1.5 years of treatment. There is disease relapse after stopping the drug but no rebound flare, and no loss of

efficacy on restarting ustekinumab. The short- to medium-term side-effects profile is no different than that of placebo, though long-term safety data remain unclear because the drug is new.

The drug is convenient to use requiring an injection at 0, 4 and then every 12 weeks.

Initially ustekinumab is likely to be used by clinicians as a second-line agent to TNF-alpha antagonists. However, for patients that meet current the current NICE criteria for the use of biologic agents in psoriasis but have become unresponsive or are resistant to TNF-alpha antagonists, or where they

are contraindicated on grounds not shared with ustekinumab, then ustekinumab would certainly be the treatment of choice.

#### References

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