

Research Review™

Ustekinumab [Stelara™] Review

Making Education Easy

2010

In this review:

- Psoriasis description and treatment approaches
- About ustekinumab
- Major safety and efficacy studies of ustekinumab
 - PHOENIX 1/2
 - ACCEPT
- Lessons learned from targeting IL-12/23
- Efficacy and tolerability of biologics vs. nonbiologics

Research Review publications are intended for Australian health professionals.

Psoriasis

Psoriasis is a chronic, relapsing, noninfectious, immune-mediated disease with several different clinical variants.^{1,2} The most common variant is plaque psoriasis, which is characterised by circular or oval erythematous, scaly plaques involving extensor body surfaces and the scalp. Other variants include flexural psoriasis, guttate psoriasis, pustular psoriasis, nail psoriasis, erythrodermic psoriasis and psoriatic arthritis (which affects 10–20% of patients with plaque psoriasis). There are two age ranges at which appearance of the disease peaks (16–22 years and 57–60 years) with females and those with a family history often having an earlier onset age. There is a strong genetic basis for the disease, and it's prevalence in Caucasian Australians reflects that of the Western World at around 2.6%, while Australian Aborigines are not affected.³ The pathogenesis of psoriasis is believed to involve abnormalities in immune function, including antigen presentation activation of T-cells and macrophages, and cytokine release, specifically interleukin (IL)-12 and IL-23.⁴

Current Treatment Approaches

Psoriasis is often a difficult disease to treat, requiring a long-term pharmacotherapeutic regimen that is best tailored to patients' specific expectations rather than to the extent of their disease.^{1,2} First-line psoriasis treatment usually consists of topical corticosteroids and/or vitamin D analogue, with keratolytics added if compatible. Phototherapy is usually reserved for patients with extensive, widespread psoriatic lesions. Systemic agents are normally started if both topical treatments and phototherapy have failed. Surgery has no place in psoriasis management.

Biologic therapies are still indicated relatively new treatments for psoriasis, and are generally considered only for severe, refractory disease when other treatments have failed, and also for patients with active psoriatic arthritis in addition to psoriatic plaques.¹ Biologic agents act on the following key steps in psoriasis pathogenesis: 1) inhibition of initial cytokine release and Langerhans cell migration; 2) prevention of T-cell activation by 'antigen presenting cells and elimination of pathogenic T-cells; 3) blocking interactions that result in T-cell activation or migration into tissue; 4) modification of the T-cell type balance; and 5) inhibition of cytokines tumour necrosis factor (TNF) and IL-12 and IL-23.

Patient satisfaction and adherence to psoriasis treatment are important to consider, as these are often barriers to effective management.² Biologic agents have the best adherence rate. As well as a substantial burden on healthcare systems, psoriasis has a similar impact on patients' health-related quality of life (QOL) as other major medical conditions, including their perception of general health and social functioning.^{5,6} QOL is therefore an important consideration in psoriasis management.

About ustekinumab

Ustekinumab is a fully human monoclonal antibody that binds to the subunit of p40 the cytokines IL-12 and IL-23 with high specificity, thereby inhibiting IL-12 and IL-23 receptor-mediated signalling.⁷ Dose-dependent clinical responses to SC and IV ustekinumab in patients with psoriasis were first observed in two phase I trials, both of which also demonstrated a good safety profile and linear pharmacokinetics.^{8,9} Data from the PHOENIX 1 and 2 and ACCEPT RCTs have shown SC ustekinumab to be effective, with improved clinical and QOL parameters, and generally well tolerated for the treatment of moderate-to-severe plaque psoriasis; findings from these RCTs are presented in this review.^{10–14} A phase 2 trial in patients with active plaque psoriasis and psoriatic arthritis has also shown SC ustekinumab to be associated with greater improvements in the signs and symptoms of the disease and QOL scores than placebo.¹⁵

Ustekinumab was first approved for use in Canada in late 2008, and then in the US and Europe in 2009, for patients aged ≥18 years with moderate or severe psoriasis.^{16–18} In Australia, ustekinumab is currently available on the Pharmaceutical Benefits Scheme (PBS) as an authority required benefit for systemic monotherapy in adults with severe chronic plaque psoriasis.¹⁹ The recommended dosage in Australia is 45mg administered by SC injection at weeks 0 and 4, and thereafter every 12 weeks. The dose can be doubled to 90mg for patients with a bodyweight >100 kg; even though 45mg is efficacious in this patient group, efficacy is greater with the higher dose. This regimen is consistent with those advised by Health Canada, the European Medicines Agency and the US FDA.

Major safety and efficacy studies of ustekinumab

The IL-12 family member p40 chain as a master switch and novel therapeutic target in psoriasis²⁰

Authors: Nestle FO & Conrad C

Comment: This editorial commented upon the first report of ustekinumab use in patients with chronic plaque psoriasis. Psoriasis is a common T-cell mediated inflammatory disease of humans, often referred to as autoimmune, but, like rheumatoid arthritis and Crohn's disease, lacks a known auto-antigen. Lesional and/or circulating T-cell activation and subsequent cytokine production result in keratinocyte hyperproliferation and angiogenesis. TNF is considered the master cytokine relevant to the disease process, and is found in increased amounts, along with interferon, in lesional psoriatic skin. The p19 and p40 proteins (the two subunits of IL-23, p40 is also a part of IL-12) are increased in psoriatic lesions. IL-23 binds to the IL-12Rβ1/IL-23R heterodimeric receptor and activates a spectrum of Janus kinase molecules, resulting in STAT3/STAT4 heterodimers compared with IL-12, which binds to IL-12Rβ1/IL-12Rβ2 receptors resulting in STAT4 homodimer induction. A single infusion of a monoclonal antibody to p40 was well tolerated and induced concentration-dependent improvement in psoriatic lesions. This phase 1 study suggests anti-IL-12/23 p40 represents an exciting new therapeutic target in patients with chronic plaque psoriasis. The authors comment on the need for information on long-term safety, repeated infusions and antibody development, as well as further research to obtain an understanding of the relationship between dendritic cells, T-cells and keratinocytes in psoriasis.

A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis²¹

Authors: Krueger GG et al

Summary: This phase 2 double-blind, placebo-controlled study undertaken at 46 centres worldwide examined the week 12 PASI 75 and PASI 90 responses of patients with moderate-to-severe chronic plaque psoriasis to either a single dose of ustekinumab (45mg or 90mg) or 4 weekly doses of ustekinumab (45mg or 90mg) compared with placebo. Sufficiently significant numbers of patients demonstrated a sustained and marked improvement in their PASI scores, with no statistically significant increase in adverse events or serious adverse events over placebo to warrant further development of this first-in-class human monoclonal antibody.

Comment: The findings demonstrated the therapeutic efficacy and adverse event profile of an interleukin-12/23 monoclonal antibody in the treatment of psoriasis and established a central role for the antigen presenting cell-produced IL-12/23 p40 cytokines in the pathophysiology of psoriasis. Patient-reported outcome measures and QOL improvements mirrored the objective investigator assessments. Many patients indicated that their psoriasis had no detectable adverse effect on their QOL after receiving active treatment. Although tuberculosis and opportunistic infections have been reported in persons with congenital deficiency of IL-12 p40 or IL-12 receptor β1, none were reported in the study. The trial was not designed to evaluate the efficacy and safety of long-term use. The authors remarked that additional studies were required to characterise the safety and efficacy profile of ustekinumab and to define the appropriate schedule that would maintain the high level of response safely.

Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1)¹⁰

Authors: Leonardi CL et al, for the PHOENIX 1 study investigators

Summary: SC ustekinumab 45 and 90mg on weeks 0 and 4 was a superior treatment at 12 weeks compared with placebo in patients with moderate-to-severe psoriasis. Moreover, efficacy was maintained in most patients for ≥ 1 year with continued 12-weekly ustekinumab injections.

Methods: Patients aged ≥ 18 years with moderate-to-severe plaque psoriasis (PASI score ≥ 12 , $\geq 10\%$ body surface area involvement and candidates for photo- or systemic therapy), which had been diagnosed ≥ 6 months earlier, were enrolled in a double-blind, placebo-controlled, multicentre RCT with the following three phases:

- 1) 12-week placebo-controlled phase
 - participants were randomised to receive ustekinumab 45mg (n=255) or 90mg (n=256) at weeks 0 and 4, or placebo (n=255)
- 2) 28-week placebo-crossover and active treatment phase (study weeks 12–40)
 - phase 1 placebo participants were further randomised to receive ustekinumab 45mg or 90mg at weeks 12 and 16, and then every 12 weeks
 - phase 1 ustekinumab recipients continued their respective doses of the agent every 12 weeks
 - participants discontinued at study week 28 if they had not achieved PASI 50
 - the dosing interval was decreased to 8 weeks for participants who had achieved only PASI 50–75 at study week 28
- 3) 36-week randomised withdrawal phase (study weeks 40–76)
 - participants who received ustekinumab in phase 1 and had achieved long-term efficacy (PASI 75) were re-randomised to continue treatment at their previously assigned dose or switched to placebo
 - phase 1 placebo group were switched back to placebo
 - participants who had not achieved PASI 75 at week 40 either discontinued treatment or the dosing interval was decreased to 8 weeks
 - participants re-randomised to, or restarted, placebo at week 40 restarted active treatment if they lost $\geq 50\%$ of their PASI improvement.

Results: At week 12, a significantly greater proportion of participants randomised to receive ustekinumab 45mg and 90mg had achieved PASI 75 (primary endpoint) than those who received placebo (67.1% and 66.4%, respectively, vs. 3.1%; $p < 0.0001$). While response was

maintained at week 40 in 160 and 162 phase 1 ustekinumab recipients who had continued and discontinued active treatment, respectively, the PASI 75 response rate was significantly superior at 1 year in responders who continued maintenance therapy compared with those who were switched to placebo at week 40 ($p < 0.0001$). Ustekinumab recipients also consistently had better PGA and DLQI scores, which mirrored improvements in PASI scores, than placebo recipients; improvements in DLQI scores were evident as early as week 2. Adverse events were reported in 54.5% (serious 1.2%) and 48.2% (serious 0.8%) of ustekinumab and placebo recipients, respectively, during the placebo-controlled phase; the adverse event profiles for the other phases were similar.

Comments:

- The PHOENIX 1 study provided 18-month data on the tolerability and efficacy of ustekinumab in the management of chronic plaque psoriasis. Two thirds of participants, with a mean baseline PASI of 20, demonstrated at least a 75% improvement in this score at week 12, eight weeks after their second SC injection. Over one-third improved at least 90%. Maximal response to therapy was seen at week 24.
- Latent tuberculosis was diagnosed at or before screening in 25 patients who were treated with isoniazid and entered the study without reactivation of their tuberculosis.
- The median percentage improvement in PASI score remained stable out to week 76 in patients receiving 12-weekly SC injections. No rebound was reported upon withdrawal of therapy, with median time to loss of PASI 75 approximately 15 weeks.
- Over half the treated patients achieved a DLQI score of zero or one by week 12, equating to psoriasis having no impact on QOL in these individuals. Response in the DLQI was maintained out to week 76 in patients continuing on therapy.
- Low titre antibodies were detected in 5.1%, but were not associated with loss of efficacy or injection-site reactions.
- Rates of infections in the treatment group were not greater than in the placebo group, and rates of serious infection, cutaneous and noncutaneous malignancies, and cardiovascular events were low out to week 76, with no increase over time. The main adverse events were upper respiratory tract infections, nasopharyngitis, headache and arthralgia.
- The results indicate a potentially important therapeutic agent for the treatment of patients with chronic plaque psoriasis.

Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)¹¹

Authors: Papp KA et al

Summary: The efficacy of ustekinumab 45 and 90mg every 12 weeks in patients with moderate-to-severe plaque psoriasis seen in PHOENIX 1 was confirmed in this RCT. Furthermore, dose intensification to 90mg every 8 weeks was shown to produce a response in participants who only partially responded to the initial regimen.

Methods: Patients aged ≥ 18 years with plaque psoriasis (PASI score ≥ 12 , $\geq 10\%$ body surface area involvement and candidates for photo- or systemic therapy) that had been diagnosed ≥ 6 months earlier were enrolled in a double-blind, placebo-controlled, multicentre RCT with the following three phases:

- 4) 12-week placebo-controlled phase
 - participants were randomised to receive ustekinumab 45mg (n=409) or 90mg (n=411) at weeks 0 and 4, or placebo (n=410)
- 5) 16-week placebo-crossover and active treatment phase (study weeks 12–28)
 - phase 1 placebo recipients were further randomised to receive ustekinumab 45mg or 90mg at weeks 12 and 16, and then every 12 weeks
 - phase 1 ustekinumab recipients continued their respective doses of the agent every 12 weeks
- 6) 24-week randomised dose-intensification phase (study weeks 28–52)
 - phase 1 ustekinumab partial responders (PASI 50–75) at study week 28 were randomised to continue receiving their assigned dose of the agent at the same 12-week frequency or every 8 weeks
 - phase 1 ustekinumab responders (PASI 75) continued treatment at the same dose and frequency
 - nonresponders (PASI < 50) discontinued treatment
 - participants who received placebo during phase 1 continued their assigned phase 2 ustekinumab treatment every 12 weeks

Results: At week 12, a significantly greater proportion of participants randomised to receive ustekinumab 45mg and 90mg had achieved PASI 75 (primary endpoint) than those who received placebo (66.7% and 75.7%, respectively, vs. 3.7%; $p < 0.0001$ for both comparisons). The onset of efficacy was apparent among ustekinumab recipients as early as week 2, and improvements were generally sustained out to 52 weeks among those who had responded at 12 weeks. Ustekinumab recipients also consistently had better PGA and DLQI scores than placebo recipients.

The proportion of partial responders who had achieved PASI 75 by week 52 was significantly greater for those in the 90mg dose group who switched to 8-week dosing for phase 3 of the trial compared with those who continued 12-week dosing (68.8% vs. 33.3%; $p = 0.004$), as was the mean number of visits with PASI 75 response (2.63 vs. 1.58; $p = 0.014$). In contrast, these endpoints were similar in the 8- and 12-week dosing groups for those receiving ustekinumab 45mg. During the placebo-controlled phase, adverse events were reported in 53.1% (serious 2.0%) and 47.9% (serious 1.2%) of ustekinumab 45mg and 90mg recipients, respectively, and in 49.8% (serious 2.0%) of the placebo recipients.

Comment: The PHOENIX 2 study reported 12-month results on the efficacy and tolerability of ustekinumab in the management of chronic plaque psoriasis. Whereas PHOENIX 1 examined the effect of treatment interruption at week 40, PHOENIX 2 looked at dose optimisation at week 28. Efficacy results in PHOENIX 2 were remarkably similar to PHOENIX 1, with at least two-thirds of participants (with a baseline PASI of around 20 and baseline body surface area $> 25\%$) achieving at least a 75% improvement in PASI score at week 12. Again, maximum response was seen at around week 24. Participants receiving placebo for the first 12 weeks (like in the PHOENIX 1 study) achieved a response similar to the active treatment group after crossover to ustekinumab. Response rates at week 28 were identical for PASI 75 response, PGA response and median PASI improvement. Rates of serious infection in the active and placebo groups were similar in the placebo-controlled phase of the study. Injection-site reactions occurred in 1% of ustekinumab injections and 0.4% of placebo injections. There were no anaphylactic or serum sickness-like reactions, and no cases of tuberculosis, lymphoma or demyelinating disease had developed by week 52. No dose response was observed in the frequency of adverse events, serious adverse events or adverse events leading to discontinuation. Anti-ustekinumab antibodies developed in 5.4% of participants; a higher frequency was seen in partial responders (50% to $< 75\%$ improvement in PASI) at week 52 compared with PASI 75 responders. Serum ustekinumab trough concentrations were lower (on average) in partial responders than in PASI 75 responders. Partial responders tended to have higher bodyweight, more severe disease (as measured by PGA) and a higher frequency of psoriatic arthritis. They were also more likely to have used and/or failed treatment with conventional systemic or other biologic agents. Dose intensification resulted in higher mean trough drug concentrations. PASI 75 response was achieved in more partial responders receiving 90mg who had a reduced dosing interval (but not in the 45mg group) than those who continued on 12-weekly dosing. The authors concluded that ustekinumab was an effective treatment for most patients with moderate-to-severe psoriasis if received every 12 weeks, but partial responders may benefit from an 8-week dosing interval.

Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis¹⁴

Authors: Griffiths CEM et al

Summary/comment: The ACCEPT study was the first RCT to compare two biologic agents in patients with moderate-severe chronic plaque psoriasis (mean BSA 25%, mean PASI score 20). Ustekinumab 45mg or 90mg at weeks 0 and 4 showed superior efficacy to the market-leading biologic, etanercept, at a dose of 50mg twice weekly (only available on the PBS as 50mg once weekly) at week 12 when determined by PASI 75 and/or PGA evaluation. Week 12 PASI 75 responses for ustekinumab were similar to that seen in the PHOENIX 1 and 2 trials, with 67% and 74% achieving this level of response for 45mg and 90mg, respectively, while 57% of etanercept-treated patients reached this benchmark. Onset of response was more rapid in those treated with ustekinumab. After crossover to ustekinumab, 49% of patients who did not have a response to etanercept achieved PASI 75 within 12 weeks. Rates of adverse

events, discontinuation due to adverse events, and serious adverse events through the 12-week comparison were similar for the two agents. Injection-site reactions were more common with etanercept (25%; 24 injections in 12 weeks) compared with ustekinumab (4%; two injections), and typically were mild with no anaphylaxis or serum sickness-like reactions. Three patients treated with ustekinumab had nonmelanoma skin cancer (NMSC) detected in areas of cleared psoriasis by week 12. Patients achieving a PGA of clear, minimal or mild (≤ 2) at week 12 had treatment interrupted until psoriasis recurred (moderate, marked, severe), with median times to recurrence of 14.4, 18.1 and 7.3 weeks for those treated with ustekinumab 45mg and 90mg and etanercept, respectively. Upon reintroduction of ustekinumab, 84% reached PGA ≤ 2 within 8 weeks.

The ustekinumab safety experience in patients with moderate-to-severe psoriasis: results from pooled analyses of phase 2 and phase 3 clinical trial data¹²

Authors: Gordon K et al

Summary: The cumulative safety of ustekinumab among individuals who were exposed to at least one dose in phase 2 and 3 trials was favourable and remained consistent without evidence of cumulative toxicity over study periods of up to 18 months duration. A similarly favourable safety profile was seen in the ustekinumab clinical safety database of patients treated with the agent for ≤ 3 years.

Methods: Safety data were collated from a phase 2 RCT and the PHOENIX 1 and 2 RCTs.^{10,11,21} Each trial investigated ustekinumab 45mg and 90mg, with a single injection compared with weekly injections in the phase 2 trial; the protocols for the two phase 3 PHOENIX trials are described on page 2. A 3-year safety analysis based on all data available up until May 2009 included 36-, 152- and 100-week data from the phase 2, PHOENIX1 and PHOENIX 2 trials, respectively and 64 weeks of data from the ACCEPT trial.¹⁴ Adverse events of interest included infections (serious and those requiring antibiotic treatment), malignancies and major cardiovascular events (sudden cardiac death, serious myocardial infarction events and serious stroke events).

Results: There were 2266 study participants with 2251 patient-years of follow-up included in the 18-month safety analysis and 3117 participants with 4782 patient-years of follow-up in the 3-year safety analysis. During the trials' 12-week placebo-controlled periods, ≥ 1 adverse events were reported in 57.6% (serious 1.6%) and 51.6% (serious 1.4%) of ustekinumab 45mg and 90mg recipients, respectively, and in 50.4% (serious 1.4%) of the placebo recipients. For the 18-month analysis, ≥ 1 adverse events occurred in 85.7% (serious 5.9%) and 82.0% (serious 4.7%) of ustekinumab 45mg and 90mg recipients, respectively, and the respective rates for adverse events leading to treatment discontinuation were 3.2% and 2.9%. Moreover, there was no evidence of these rates disproportionately increasing over time or with extended duration of drug exposure. Rates/incidences for events of interest also did not increase with time or duration of ustekinumab therapy (see Table).

Comment: Close to 2000 patients had received ≥ 6 months of therapy. Rates of adverse events, serious adverse events, infections and adverse events leading to study drug discontinuation did

not increase out to 3 years. During the placebo-controlled period, there was no dose-related effect on adverse events, including infections, and the rates were no higher in those receiving active therapy than the placebo group. Rates of serious infection and infections requiring antimicrobial treatment were low and remained low with no evidence of increase associated with prolonged exposure or increased cumulative dose. Rates of NMSC and non-NMSC malignancies were not found at higher rates during the placebo-controlled period or with increasing duration of exposure. Rates of NMSC malignancies with 3 years of therapy were consistent with rates expected in the general population.

Extended use of ustekinumab was not associated with increased rates of major cardiovascular events. These events maintained a low and stable frequency, consistent with expected rates. Adverse events did not increase in frequency throughout 3 years of continuous therapy. There was no evidence of cumulative toxicity. The risk-benefit profile of ustekinumab appears favourable. Ongoing studies will provide 5-year data.

	Ustekinumab 45mg			Ustekinumab 90mg			Ustekinumab combined			Placebo
	PCP	18-mo	3-y	PCP	18-mo	3-y	PCP	18-mo	3-y	PCP
Serious infections	0.49	1.08	0.82	1.97	1.05	1.50	1.23	1.07	1.19	1.70
Infections requiring antibiotics	37.4*	37.2*	34.9*	38.8*	36.0*	34.7*	38.1*	36.6*	34.8*	36.2*
NMSC malignancies	0.49	0.63	0.64	0.98	0.97	0.77	0.74	0.80	0.71	1.13
Non-NMSC malignancies	0.49	0.63	0.69	0.00	0.09	0.46	0.25	0.36	0.57	0.57
Major CV events	0.98	0.54	0.41	1.47	0.35	0.35	1.23	0.44	0.38	0.00

CV=cardiovascular; NMSC=nonmelanoma skin cancer; n.a.=not applicable; PCP=placebo-controlled period

Table. Rates/incidences of adverse events of interest (values are rates of per 100 patient-years, expect for *incidence)

Comparison of hospitalization and serious infection rates among patients with moderate to severe psoriasis treated with ustekinumab: comparisons with a large healthcare claims database¹³

Authors: Healy E et al, on behalf of the PHOENIX 1 and PHOENIX 2 investigators

Summary: The rates of hospitalisation and serious infections among patients with psoriasis treated with ustekinumab in phase 1–3 trials were not greater than expected rates for patients with psoriasis based on data from a healthcare claims database.

Methods: Rates of hospitalisation and serious infections were compared between: a) 2301 participants from phase 1–3 ustekinumab trials (1480 patient-years of follow-up); and b) 1183 patients (mean age 54.4 years; 50% female) with a psoriasis claim (ICD-9 CM 696.x.) in a US healthcare claims database who received treatment with systemic agents or psoralen plus ultraviolet A therapy in both 2003 and 2004.

Results: The rates of hospitalisation (≥ 1 hospitalisation during 2004) and serious infections (identified from inpatient diagnoses) among the patients from the healthcare claims database were 11.3 and 2.2 per 100 patients-years, respectively; however, these rates were greater for females versus males and for older versus younger patients. After adjusting these rates for age and sex, they were not lower than the respective observed rates among the 2301 ustekinumab trial recipients (see figure).

Comment: The authors compared the frequency of hospitalisation and serious infection in patients with psoriasis treated with ustekinumab and patients with moderate-to-severe psoriasis from a large US healthcare database. Rates of hospitalisation and serious infection were higher in the health claims database than in patients treated with ustekinumab, even after adjusting for

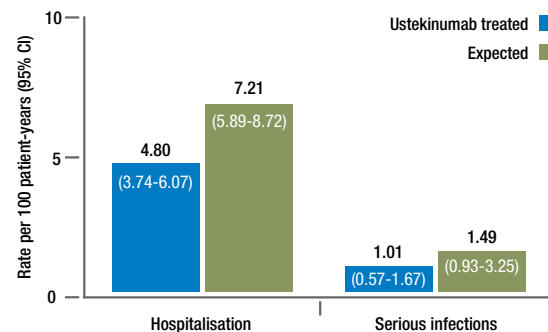


Figure 1. Rates of hospitalisation and serious infections among trial participants with psoriasis treated with ustekinumab versus expected age- and sex-adjusted healthcare claims database rates for patients with psoriasis

age-sex distribution, even though this was not statistically significant. These data are reassuring, as previous comparisons have been for only 12 weeks in a placebo-controlled setting, and are consistent with the 3-year data that show no increase in infections over time.

Ustekinumab: Lessons learned from targeting interleukin-12/23 p40 in immune-mediated diseases²²

Authors: Elliott M et al

Summary/comment: IL-12/23 p40 has been shown in preclinical disease models to be important in the pathogenesis of several immune-mediated disorders. There are strong genetic associations between psoriasis and polymorphisms of both the IL-12 gene, which encodes the p40 subunit, and the IL-23R gene, which encodes the IL-23R receptor subunit. The p40 subunit of IL-12 and IL-23 are overexpressed in psoriatic plaques, and IL-23 p19 is also expressed in increased amounts in psoriatic lesions. Other translational data in immune-mediated diseases, including psoriatic arthritis, Crohn's disease and multiple sclerosis, also support the development of ustekinumab. Ustekinumab, effective in nonhuman experimental autoimmune encephalitis, was ineffective in treating patients with multiple sclerosis. It was safe and well tolerated, and did not exacerbate inflammatory demyelination. Early studies in Crohn's disease suggest a favourable clinical response for ustekinumab with no increase in adverse events. This review commented upon the excellent efficacy of ustekinumab in psoriasis, suggesting a key role of the Th1/Th17 pathways in this disease, with a favourable risk-benefit profile.

Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis²³

Authors: Schmitt J et al

Summary/comment: This meta-analysis based on the examination of 24 RCTs (before data were published on ustekinumab) questioned the nature for current regulatory guidelines recommending biologics as second-line therapy for moderate-to-severe chronic plaque psoriasis. The efficacy responses, improvement in QOL and tolerability for biologics were not inferior to traditional systemic agents, and in many cases were found to be more favourable. The differences in response rates of the examined biologic treatments tended to become less pronounced with increasing duration of treatment, although the evidence became weaker with longer time periods. The review highlighted the great lack of key comparative data and of data related to long-term safety and efficacy of biologic and nonbiologic treatments for moderate-to-severe chronic plaque psoriasis. The authors stated their hopes that recently established registries will gather valid and generalisable evidence to answer some of these unasked questions. They also encouraged head-to-head long-term RCTs to compare different agents.

References

- Lui H & Mamelak AJ. Plaque Psoriasis. emedicine from WebMD; Medscape. Updated 30 Sept 2009. Available from <http://emedicine.medscape.com/article/1108072-overview>
- Wu Y et al. Poor patient satisfaction and medication adherence among patients with psoriasis: results from a large national survey. *Psoriasis Forum* 2007;13(2):22–6
- Raychaudhuri SP & Farber EM. The prevalence of psoriasis in the world. *J Eur Acad Dermatol Venereol* 2001 15(1):16–7
- Boker A et al. Biologics in the treatment of psoriasis. *Curr Opin Invest Drug* 2007;8(11):939–46
- Rapp SR et al. Psoriasis cases as much disability as other major medical conditions. *J Am Acad Dermatol* 1999;41(3 Pt. 1):401–7
- Weiss SC et al. Quantifying the harmful effect of psoriasis on health-related quality of life. *J Am Acad Dermatol* 2002;47(4):512–8
- Reddy M et al. Modulation of CLA, IL-12R, CD40L, and IL-2R α expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. *Cell Immunol* 2007;247(1):1–11
- Kauffman CL et al. A phase I study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis. *J Invest Dermatol* 2004;123(6):1037–44
- Gottlieb AB et al. A phase 1, double-blind, placebo-controlled study evaluating single subcutaneous administrations of a human interleukin-12/23 monoclonal antibody in subjects with plaque psoriasis. *Curr Med Res Opin* 2007;23(5):1081–92
- Leonardi CL et al, for the PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; 371(9625):1665–74
- Papp KA et al, for the PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371(9625):1675–84
- Gordon K et al. The ustekinumab safety experience in patients with moderate-to-severe psoriasis: results from pooled analyses of phase 2 and phase 3 clinical trial data. Poster presentation P1170; 18th Congress of the European Academy of Dermatology and Venereology. ICC Berlin, Oct 7–11 2009
- Healy E et al, on behalf of the PHOENIX 1 and PHOENIX 2 investigators. Comparison of hospitalization and serious infection rates among patients with moderate to severe psoriasis treated with ustekinumab: comparisons with a large healthcare claims database. Poster presentation P15; 89th Annual Meeting of the British Association of Dermatologists. Glasgow SECC, Jul 7–10 2009
- Griffiths CEM et al. A phase 3, multicenter, randomized study comparing ustekinumab and etanercept for the treatment of moderate to severe plaque psoriasis. Abstract no. FP 1336 plus poster; 17th Congress of the European Academy of Dermatology and Venereology. Paris, Sep 17–21 2008
- Gottlieb A et al. Ustekinumab, a human interleukin 12/ 23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009;373(9664):633–40
- Health Canada. Consumer Information: Product Monograph Part III "STELARA; ustekinumab. Available from http://www.hc-sc.gc.ca/dhp-mpps/alt_formats/hpfb-dgspa/pdf/prodpharma/pm_mp_2008_stelara_114272_partiii-eng.pdf
- US FDA. Highlights of Prescribing information: Stelara™ (ustekinumab). Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125261lbl.pdf
- EMA. Stelara: ustekinumab: EPAR summary for the public. Available from <http://www.ema.europa.eu/humandocs/PDFs/EPAR/stelara/H-958-en1.pdf>
- Medicare Australia, Specialised drugs PBS. Severe chronic plaque psoriasis. Available from <http://www.medicareaustralia.gov.au/provider/pbs/drugs2/psoriasis.jsp>
- Nestle FO & Conrad C. The IL-12 family member p40 chain as a master switch and novel therapeutic target in psoriasis. *J Invest Dermatol* 2004;123(6):xiv–xv
- Krueger GG et al, for the CNTO 1275 Psoriasis Study Group. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007;356(6):580–92
- Elliott M et al. Ustekinumab: lessons learned from targeting interleukin-12/23p40 in immune-mediated diseases. *Ann N Y Acad Sci* 2009;1182:97–110
- Schmitt J et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis. *Br J Dermatol* 2008;159(3):513–26

Ustekinumab [Stelara™] Review

Independent commentary by Associate Professor Peter Foley.

Graduated: BMedSc, Monash University, 1985; MBBS, Monash University, 1987; MD, The University of Melbourne, 1996; Fellowship, The Australasian College of Dermatologists (FACD) 1997

Present Positions: Private Dermatology Practice Malvern East; Visiting Dermatologist, St. Vincent's Hospital Melbourne; Associate Professor, The University of Melbourne, Department of Medicine (Dermatology); Visiting Dermatologist, Skin and Cancer Foundation (Victoria)

Convenor, Scientific Advisory Committee, The Australasian College of Dermatologists; President, Skin and Cancer Foundation (Victoria); Board of Directors, Photomedicine Society; Steering Committee, GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis), Member Dermatology Medical Advisory Boards for Abbott, Janssen-Cilag, MSD (Schering-Plough), Pfizer (Wyeth)

Research Review is an independent medical publishing organisation producing electronic journals in several specialist areas. These journals provide summaries of the 'must see' studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter. Research Review publications are intended for Australian medical professionals.

Privacy Policy: Research Review will record your email details on a secure database and will not release it to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Disclaimer: This publication has been created with support funding from Janssen-Cilag. The content is entirely independent and based on published studies and the author's opinions.