Ustekinumab: a more selective and effective treatment of psoriasis

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease affecting approximately 2% of the world's population. Therapeutic agents used for the management of psoriasis commonly target the underlying inflammation. Biologic agents that selectively block the steps in the inflammatory cascade have provided additional therapies for psoriasis. Pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α) play a central role in the inflammation underlying psoriasis and anti-TNF-α therapies have been proved highly effective in treating psoriasis in the past seven years. More recently, interleukin (IL) -12 and IL-23, cytokines that drive naive CD4+ lymphocytes into type 1 helper T cells (Th1 cells) and type 17 helper T cells (Th17 cells) respectively, have been identified as key mediators of psoriasis. A new class of biologic agent, ustekinumab, a fully human monoclonal antibody which selectively targets the p40 subunits of IL-12 and IL-23, has been approved in Europe, the United States and Hong Kong for the treatment of plaque psoriasis in patients who fail to respond to, or have a contraindication to other systemic therapies. The efficacy and short term safety of ustekinumab in the treatment of psoriasis has been demonstrated in three large phase three studies: PHOENIX 1, PHOENIX 2 and ACCEPT. Both PHOENIX 1 and PHOENIX 2 were discussed in details during the talk. The PHOENIX 1 (76-week study) was the treatment efficacy study. Ustekinumab 45 mg and 90 mg in two treatment arms were given at week zero, four, and then every 12 weeks with subsequent crossover of the placebo arm to treatment arm were taken at week 12. In PHOENIX 2 (52-week study), dose intensification to ustekinumab 90 mg every 8 weeks were studied in the partial responders. Both PHOENIX 1 and PHOENIX 2 are currently ongoing with five years of patients follow-up planned.

Efficacy of ustekinumab

In PHOENIX 1, 67% of patients receiving ustekinumab 45 mg and 66% receiving ustekinumab 90 mg (dosing at week 0 and 4) achieved the primary endpoint of PASI 75 at week 12, compared with only 3% receiving placebo. Efficacy continued to improve with 71% (45 mg dose) and 79% (90 mg dose) of the patients attaining PASI 75 at week 40.

In the ongoing studies of PHOENIX 1 (3-year) and PHOENIX 2 (2-year), about 20% of subjects discontinued from the active treatment due to various reasons: adverse events (5%), unsatisfactory therapeutic response (2%), non-responder per protocol (4%), lost to follow up (2%) and others (6%). As a result, about 80% of the responders continued to receive

ustekinumab in the ongoing studies and the PASI 75 response was stable through week 148.

For dosage adjustment study in PHOENIX 2, 50-65% of the subjects who were either partial responder (PASI 50-75) at week 28 or PASI 75 non-responder at week 40 attained a PASI 75 response after adjusting the dosing to every 8 weeks and the clinical response remained stable through week 148.

Safety of ustekinumab

From the analysis of the 3-year safety data in 2009, there were over 3000 patients exposed to ustekinumab in which 157 patients had been using the medication for over 3 years.

Overall safety

Infections of all causes were observed in 48% of the patient receiving ustekinumab, majority of them being upper respiratory tract infection. Serious adverse events were observed in up to 5% of the treatment patients. However, these adverse events might or might not be directly related to the administration of ustekinumab, as a result, targeted safety data was more relevant for interpretation.

Targeted safety

Major safety concern for biological agents was serious infection and malignancy. Three year safety data was available for analysis.

The combined incidence of serious infection was 1.19 per 100 patient-years (95% CI 0.90-1.54) whereas the corresponding figure for the control group was 1.70 per 100 patient-years (95% CI 0.35-4.96).

There was one reported case of pulmonary tuberculosis (TB) in Taiwan, in which the patient had negative baseline tuberculin skin test and γ-interferon assay. However, pulmonary shadow was present in the baseline chest X-ray. No other reported case of tuberculosis was found in the 97 subjects with latent TB who were treated with isoniazid before commencing ustekinumab. No environmental mycobacterial infection, salmonella or systemic fungal infection were reported. There were no excessive increase risks in non-melanoma skin cancer, solid organ tumours and cardiovascular events when compared to controls or expected rates in the general population.

Antibodies to ustekinumab were reported in 3.8%-5.4% in 52-152 weeks in different clinical trials. There was no reported case of anaphylaxis or serum-sickness like reactions to ustekinumab.

Learning points

IL-12/23 are novel targets for the treatment of psoriasis. The first anti-IL-12/23 antibody, ustekinumab, was shown to be highly effective in three large phase three clinical trials. Only three years safety data was available at this moment. Important safety issues such as serious infection and malignancy remained consistent with the expected rate in the general population. Longer follow-up period is needed to clarify the issues in efficacy maintenance and safety for this novel biological treatment.