TRIAL WATCH

Novel biologic for psoriasis shows superiority over current best-seller

A Phase III trial of Johnson and Johnson's investigational drug ustekinumab in patients with moderate to severe psoriasis has shown that it is more effective — and requires far fewer injections — than etanercept (Enbrel; Amgen/Wyeth).

In the 12-week study, reported at the 17th meeting of the European Academy of Dermatology and Venereology (abstract FP1336), ustekinumab (45 mg or 90 mg), given by injection at the start of the study and again at 4 weeks, was compared with etanercept, which was given twice a week every week. In the ustekinumab groups, 68% and 74% of participants (45 mg or 90 mg dose, respectively) met the primary end point of a 75% reduction in psoriasis severity at the end of the trial compared with 57% of patients on etanercept.

A key component in the pathogenesis of psoriasis — a chronic inflammatory skin disorder characterized by red, scaly plaques — is the migration of T cells into the epidermis and release of inflammatory mediators such as tumour-necrosis factor-α (TNF-α), leading to hyperproliferation of keratinocytes. Traditional treatments for psoriasis, such as topical steroids or methotrexate, have limitations including inconvenience and toxicity, respectively. However, several novel biologics that offer more effective treatment have been approved in recent years, including the TNF-α antagonist etanercept.

Ustekinumab is a human monoclonal antibody that antagonizes signalling by the heterodimeric cytokines interleukin 12 (IL12) and IL23 by binding to their shared p40 subunit. Studies suggest that IL23 might be particularly important in psoriatic plaques (*J. Am. Acad. Dermatol.* 57, 1059–1068; 2007). It is thought that IL23 stimulates a subset of T cells to produce IL17, which then synergizes with interferon-γ (INFγ) — which facilitates T cell infiltration into the epidermis — to increase the production of pro-inflammatory cytokines by keratinocytes.

"A key need for new treatments is to move beyond disease control", says Steven Feldman, Professor of Dermatology, Pathology and Public Health Science at Wake Forest University, USA. Indeed, in the recent trial, more patients in the two ustekinumab groups achieved "cleared" or "minimal" psoriasis severity scores (65% and 71%, respectively, compared with 49% in the etanercept group). The trial also indicated a further significant benefit of ustekinumab — the intermittent, convenient dosing schedule. "Patients will value this highly," says Feldman. This was also demonstrated in two earlier placebo-controlled trials (*Lancet* 371, 1665–1674; 2008; *Lancet* 371, 1675–1684; 2008), in which the response to ustekinumab was maintained during the 12 weeks between injection times.

Although the current trial was relatively short, the two earlier placebo-controlled trials also showed that ustekinumab was well tolerated for 52–76 weeks. However, this still represents a "small safety database compared with currently available treatments such as adalimumab, etanercept and infliximab [which all target TNF-α]," says Alice Gottlieb, Chair and Dermatologist in Chief, Tufts Medical Center, Boston, USA. Lack of long-term safety data — in particular regarding the potential for malignancy — was also raised as a concern during an FDA advisory committee meeting in June 2008 (see Further information). The committee unanimously recommended approval of ustekinumab, but extended the review period until December of this year. A marketing application has also been submitted to the EMEA.

As has been demonstrated for TNF-α inhibitors, inhibiting IL12 or IL23 might also be beneficial in other immune disorders, including psoriatic arthritis — an important potential benefit, says Gottlieb, as ~30% of patients with psoriasis also have psoriatic arthritis. Several other agents targeting IL12 or IL23 for various immune disorders are also in development (TABLE 1).

Table 1 | **Development status of IL12 and IL23 antagonists***

Drug (company)	Indication	Development status
Ustekinumab (Johnson & Johnson)	Psoriasis	Preregistration
	PA, Crohn's disease, MS	Phase II
ABT-874‡ (Abbott)	Psoriasis	Phase III
	Crohn's disease	Phase II
Apilimod§ (Synta Pharmaceuticals)	RA, Crohn's disease	Phase II
	Multiple sclerosis	Preclinical

*Information (on compounds targeting the shared p40 subunit of interleukin 12 (IL12) and IL23) was obtained from the Investigational Drugs Database from Thompson Reuters. ‡Discontinued for multiple sclerosis and inflammatory disease; no development reported for autoimmune disease or rheumatoid arthritis. §Discontinued for psoriasis. MS, multiple sclerosis; PA, psoriatic arthritis; RA, rheumatoid arthritis.

FURTHER INFORMATION

FDA Advisory committee meeting:
http://www.fda.gov/ohrms/dockets/ac/cder08.html#DermatologicOphthalmicDrugs