BIOBUSINESS BRIEFS

TRIAL WATCH

Targeting IL-17A shows broad promise in autoimmune diseases

The interleukin 17A (IL-17A)-specific human monoclonal antibody AIN457, which is being developed by Novartis, has shown promising efficacy for the treatment of psoriasis, rheumatoid arthritis and chronic non-infectious uveitis in Phase II trials (*Sci. Transl. Med.* **2**, 52ra72; 2010).

IL-17A is an inflammatory cytokine that is principally produced by $CD4^+$ T helper 17 (T_H17) cells, and stimulates various immune cells to release pro-inflammatory cytokines such as tumour necrosis factor (TNF), IL-6 and IL-1. "Since the late 1990s, when we found that production of IL-6 by explants of synovium membrane from patients with rheumatoid arthritis was reduced by two-thirds by an IL-17A-blocking antibody, IL-17A has been increasingly recognized as a key mediator of T_H cell-driven autoimmune diseases," says Pierre Miossec, Professor of Clinical Immunology, Hôpital Edouard Herriot, Lyon, France.

A total of 104 patients were enrolled in the three trials, and received one or two 3–10 mg per kg doses of AIN457 (60 patients), delivered intravenously, or placebo (44 patients). In the trial involving 36 patients with chronic plaque-type psoriasis, treatment with AIN457 reduced the psoriasis area and severity index (PASI) from baseline by an average of 58% (compared with 4% in the placebo group), which was maintained at week 12. In the second trial, which involved 52 patients with rheumatoid arthritis, rapid (within 4 weeks) benefits were experienced by patients receiving AIN457, and American College of Rheumatology 20% response (ACR20) rates were 54% at week 16, compared with 31% for placebo. Lastly, in the trial involving 16 patients with the inflammatory eye disease uveitis, AIN457 treatment improved vision, reduced ocular inflammation and/or enabled cessation of corticosteroid treatment.

It is hoped that targeting IL-17A might provide additional benefits over established treatments for these diseases, such as those targeting TNF. "One-third of the rheumatoid arthritis patient population do not respond to TNF inhibition. In addition, patients can lose an initially good response to TNF inhibition and have active disease again," says Miossec. Targeting IL-17A is an attractive approach, as "IL-17A and TNF synergize to induce tissue inflammation," says Vijay Kuchroo, Principal Investigator at the Center for Neurologic Disease, Brigham and Women's Hospital, Harvard, Massachussetts, USA. AIN457 could also help to harness the immune system's regulatory mechanisms, as "IL-17A induces IL-6, which plays a crucial part in inhibiting regulatory T cell function," explains Kuchroo.

In the AIN457 trials, the rates of adverse events, including infections, were similar in the treatment and placebo groups, but larger trials with longer follow-up periods are needed to fully assess the effects of IL-17A inhibition on host defence. "IL-17A is a crucial cytokine for the control of extracellular bacterial infections and fungi," cautions Miossec. However, "blocking IL-17A for psoriasis treatment might have a lower infection risk than another emerging classes of drugs that block the IL-12 and IL-23 subunit p40, because it leaves the interferon-γ-producing T_H1 arm of immunity intact," says Kuchroo. Furthermore, IL-17A "does not appear to have a major role in the control of intracellular infections, such as tuberculosis," the reactivation of which "has been one of the major adverse events with TNF inhibition," says Miossec.