Therapeutic focus - IL-17 antibodies looking encouraging in psoriasis

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Mid-stage success for two antibodies in treating moderate to severe psoriasis may be a harbinger of a new approach to treating the inflammatory disease. The agents, Eli Lilly’s ixekizumab and Amgen’s brodalumab, target the interleukin-17 (IL-17) pathway and may offer an alternative to the tumour necrosis factor alpha (TNF-alpha) approach that has become the standard of care in treating severe autoimmune disorders.

Whilst it may be too early to say whether the IL-17 agents will result in fewer severe infections and antidrug antibodies, amongst the disadvantages of the TNF-alpha class, there is certainly a desire for more benign therapies. With three of these agents in or about to start phase III, the potential of this class will soon be known (see table).

Inflammatory response

Psoriasis is an autoimmune, inflammatory disease in which replacement of skin cells accelerates, and the oversupply of cells builds up to form raised plaques on the skin. About 2% of the world’s population suffers from the form of disease called plaque psoriasis, and 25% of these patients suffer from its moderate-to-severe form, according to the National Psoriasis Foundation.

The condition is caused by the uncontrolled activation of T helper cells, which normally act to fight infection by producing inflammatory defences. TNF-alpha is a well-validated target in combating psoriasis and the biggest selling drugs sold to treat the condition all work via this pathway – the inhibitor Enbrel and antibodies Humira and Remicade.

IL-17 meanwhile is a potent pro-inflammatory cytokine that amplifies ongoing inflammation through recruitment of neutrophils and monocytes and also enhances the formation of granulocytes. Thus, targeting the IL-17 pathway may also reduce disease severity.

Phase II data published last week in the New England Journal of Medicine found that ixekizumab, or LY2439821, and brodalumab, or AMG 827, both significantly reduced the extent and severity of the condition. The two highest doses of the Lilly drug reduced patients’ score on the psoriasis area-and-severity index (PASI) by 75% in more than 80% of cases after 12 weeks, the primary endpoint, whilst the Amgen antibody reduced the mean PASI score by more than 80% in patients taking the middle two of four doses after 12 weeks, its primary endpoint.

Both were significantly better than placebo and Mark Schoenebaum, analyst at ISI Group, commented that the data suggest these agents could be as or more effective than Enbrel, the leading biologic agent used in the moderate-to-severe plaque psoriasis patient population.

Further evidence

Data from larger trials are still needed to test the full potential of these agents. Lilly’s phase III trial in psoriasis is already underway, which could yield top line data as soon as mid-2014, according to clinicaltrials.gov. Amgen is planning its phase III, according to analysts.

The first set of phase III data is actually likely to emerge from a third candidate in the class, Novartis’ AIN457 or secukinumab; the Swiss company is currently recruiting patients in an array of inflammatory disease trials including psoriasis, ankylosing spondylitis and rheumatoid and psoriatic arthritis. First trials in psoriasis will start reporting early next year, with the biggest, a 1,264-patient trial against Enbrel, due in May 2013, according to clinicaltrials.gov.

Phase II data announced last year was similarly as encouraging – PASI 75 scores at week 12 for subcutaneous and intravenous formulations were reduced by 81% and 83% respectively.
Slight differences in the mechanism of action employed by these three agents could well yield different read outs in terms of safety and efficacy. While ixekizumab and secukinumab bind to and neutralise the actions of the IL-17 ligand, brodalumab blocks the IL-17 receptor; Amgen says this is unique in the anti-IL-17 class.

Safety data from the two phase II trials recently reported were similar. In both ixekizumab and brodalumab studies - 142 patients and 198, respectively - there were two instances on neutropenia, and in one case with brodalumab it was classed as a serious adverse event.

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*IL-17 receptor MAb
** Dual TNF MAb/IL-17A inhibitor

Earlier stage

There are a couple of earlier stage agents pursuing this approach; Roche in particular has shown some interest.

Another antibody, RG4934 from Roche is currently in phase I for psoriatic arthritis. In psoriatic arthritis pain and swelling in the joints is often coupled with psoriatic skin inflammation. Approximately 10% of patients with psoriasis also develop associated inflammation in their joints. The trial has a primary completion date of May this year according to clinicaltrials.gov.

Partnered with Roche in 2010 is Novimmune’s NI-1401 (RG7624), an anti-IL-17 monoclonal antibody that commenced the first-in-human trials at the end of last year.

Covagen also announced at the end of last year that their first drug candidate for inflammatory diseases had entered into preclinical development. The drug is a dual TNF/IL-17A inhibitor comprising of an IL-17A neutralising Fynomer - a type of small binding protein developed by Covagen - fused to an anti-TNF antibody. The Swiss company has said that the molecule preserves TNF-antibody properties while simultaneously inhibiting IL-17A and has superior efficacy to anti-TNF alone.

Other companies have tried to treat autoimmune conditions by targeting IL-17 through other means. For example vidofludimus, a small molecule drug from 4SC, inhibits the dihydroorotate dehydrogenase enzyme (DHODH), with preclinical studies indicating that the drug suppresses the expression of IL-17. Last year it failed to hit the primary endpoint in a phase Iib rheumatoid arthritis trial; more success has been seen in inflammatory bowel disease and the company is currently preparing for the phase IIb trial (4SC falls back on plan b after failure of lead compound in RA, June 09, 2011).

And in terms of new treatments for psoriasis, many believe the new oral agents in development for rheumatoid arthritis could show effectiveness in this condition. Pfizer's JAK-3 inhibitor Tofacitinib is in two phase III studies recruiting more than 1,600 patients, which should yield results next year.

Other compounds in late stage development for psoriasis include PDE4 inhibitors from Anacor Pharmaceuticals and Celgene, Abbotts IL-12 and IL-23 MAb Ozespa and Biocon's anti-CD6 MAb itolizumab. With anti-TNFs the dominant treatment for moderate to severe psoriasis, success in other classes beyond the IL-17 pathway will
be welcomed.