Ustekinumab

Ustekinumab[2] (INN, experimental name **CNTO 1275**, proprietary commercial name **Stelara**,[3] Centocor) is a human monoclonal antibody. It is manufactured in the Netherlands. It is directed against interleukin 12 and interleukin 23, naturally occurring proteins that regulate the immune system and immune-mediated inflammatory disorders.[4]

Since 2009, Ustekinumab is approved in Canada, Europe and the United States to treat moderate to severe plaque psoriasis.[5]

It has been tested in Phase II studies for sarcoidosis, (versus golimumab (Simponi)).[6]

It was found not effective for multiple sclerosis.[7]

On September 24, 2013, the FDA approved the use of ustekinumab for the treatment of psoriatic arthritis.

1 Clinical trials

1.1 Psoriasis

In two Phase III trials for moderate to severe psoriasis, the longest >76 weeks, ustekinumab was safe and effective.[8][9]

A third Phase III trial, ACCEPT, compared the efficacy and safety of ustekinumab with etanercept in the treatment of moderate to severe plaque psoriasis.[10] This trial found a significantly higher clinical response with ustekinumab over the 12-week study period compared to high-dose etanercept.[10][10]

1.2 Systemic Lupus Erythematosus

A Phase IIa trial sponsored by Janssen is a multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study of Ustekinumab in subjects with active Systemic Lupus Erythematosus.

1.3 Ankylosing Spondylitis

A clinical trial conducted in 2013 of 90 mg Ustekinumab administered subcutaneously brought a remission of Ankylosing Spondylitis in about half of the patients.[11]

2 Development

As of January 2007, there were 5 NIH-listed research studies involving CNTO 1275 on a multinational basis, including 3 Phase II and 2 Phase III trials. Three studies were focused on patients with psoriasis, one on psoriatic arthritis, and one on multiple sclerosis.

On December 4, 2007, a Biologic License Application (BLA) with the U.S. Food and Drug Administration (FDA) was filed by Centocor and Janssen-Cilag International (collaborator) has submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMEA).

In September 2008, Centocor released result of a study comparing etanercept and ustekinumab. The etanercept group received subcutaneous injections of the drug twice weekly for 12-weeks while the ustekinumab group received 2 injections, one-month apart, of either 90 or 45 milligrams. At twelve weeks, psoriatic plaques were reduced by at least three-quarters in 68% of the low-dose ustekinumab group and 74% of the high-dose group. Both groups fared better than the etanercept group, 57% of whom saw such improvement. Dr. Alan Menter, chairman of psoriasis research at Baylor Research Institute said of the results, “now we have a drug that will be used less frequently ... with a significant increase in effectiveness. These results are as good as we've seen in psoriasis.”[12]

On November 21, 2008, the European Medicines Agency’s (EMEA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for ustekinumab for the treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to other systemic therapies.[13]

On December 12, 2008 the Canadian Health Authority approved the use of ustekinumab for the treatment of chronic moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy.[13]

The FDA approved the drug on September 25, 2009 for the treatment of adult patients with moderate to severe plaque psoriasis.[14]

In November 2011, a study conducted at the Mount Sinai Medical Center in New York City by Drs. Kornbluth and Sandborn showed Ustekinumab’s potential for treating severe Crohn’s disease.[15]

3 Delivery

Patients enrolled in clinical trials of CNTO 1275 are scheduled to receive the drug by subcutaneous injections at doses of either 45 or 90 mg. The dosage and frequency varies by study and application (type of disease targeted). Generally the initial dosing interval once every three months, after the first two doses are administered four weeks apart.

4 Mechanism of action

CNTO 1275 is designed to interfere with the triggering of the body's inflammatory response through the suppression of certain cytokines. Specifically, CNTO 1275 blocks interleukin IL-12 and IL-23 which help activate certain T-cells. It binds to the p-40 subunit of both IL-12 and IL-23 so that they subsequently cannot bind to their receptors.[16]

5 Efficacy

5.1 Plaque psoriasis

In Phase III trials in patients with moderate to severe plaque psoriasis, significantly more subcutaneous ustekinumab 45 or 90 mg recipients (administered as two injections 4 weeks apart) than placebo recipients achieved a 75% improvement on the Psoriasis Area and Severity Index (PASI 75) score at 12 weeks.[17] Health-related quality of life (using the Dermatology Life Quality Index and the Health Assessment Questionnaire disability index) was improved to a significantly greater extent with ustekinumab than with placebo at week 12.[17]

5.2 Multiple sclerosis

A double-blind placebo controlled randomised dose-ranging Phase II trial in patients with RRMS (relapsing-remitting multiple sclerosis) [18] found that Ustekinumab was not efficacious in reducing the cumulative number of gadolinium-enhancing T1-weighted lesions (the primary endpoint of the study) or the number of clinical or objective relapses (the secondary endpoint). The drug was relatively well tolerated compared to placebo.[7]

6 Adverse effects

According to information provided by Centocor, maker of one medication based on ustekinumab, their version of the drug is associated with several types of serious adverse effects. These include an increased risk of infection, such as by tuberculosis and an increased risk of certain types of cancer. As with some other immunosuppressant drugs like ciclosporin, the brain swelling of posterior reversible encephalopathy syndrome is a risk. The pharmaceutical company also reports serious allergic reaction as a possible side effect. More common side effects are upper respiratory infection, headache, and tiredness.[19]

7 Pregnancy

Consult your doctor if you are pregnant or plan on becoming pregnant as it is unknown if the medication has any effects on your unborn baby. This medication may be passed into your breast milk, consult your doctor before breast-feeding.[20]

8 Tolerability

Clinical trials have shown that subcutaneous ustekinumab was generally well tolerated. Most treatment-emergent adverse events were of mild severity.[17]

9 References

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10 External links

- Centocor Ortho Biotech official site
- CNTO 1275 research studies registered with U.S. National Institutes of Health:
  - Clinical trial number *NCT00207727* for "Phase II Study on Multiple Sclerosis" at ClinicalTrials.gov
  - Clinical trial number *NCT00320216* for "Phase II Study on Psoriasis" at ClinicalTrials.gov
  - Clinical trial number *NCT00267969* for "Phase III Study on Psoriasis" at ClinicalTrials.gov
  - Clinical trial number *NCT00307437* for "Phase III Study on Psoriasis" at ClinicalTrials.gov
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