ACZ885: An Investigational Treatment in Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

What is ACZ885?

ACZ885 (canakinumab) is a selective, fully human anti-IL-1 beta monoclonal antibody. It is currently being investigated to treat Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), a rare autoinflammatory disease that can affect both children and adults[1-3]. This genetically inherited disease is characterized by long and intermittent attacks that can involve fever, abdominal pain, conjunctivitis, severe skin rash, swelling around the eyes and severe muscle and joint pain[1-3].

Under the brand name Ilaris®, ACZ885 is approved in more than 60 countries, including in the EU, US, Switzerland and Japan for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), a rare, life-long, genetic, autoinflammatory disease with debilitating symptoms[4]. CAPS is a disease that comprises three different phenotypes sharing a number of common symptoms, such as chronic recurrent fever, urticaria, occasional arthritis, deafness and potentially life threatening amyloidosis[4]:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

ACZ885 as a potential treatment for TRAPS

Mutations in *TNFRSF1A*, the gene encoding Tumor Necrosis Factor (TNF) Receptor Type 1 (TNFR1), cause the signs and symptoms associated with TRAPS. Although the exact mechanism by which these mutations lead to TRAPS symptoms is unknown, several have been suggested[5,6].

Recent evidence suggests that aside from TNF, other cytokines such as interleukin-1 beta (IL-1 beta), could play an important role in TRAPS[7]. Patients with TRAPS have shown an increased activation of NF-kappa B, a signalling molecule involved in the secretion of IL-1 beta and other proinflammatory cytokines[6,7].

Currently, there are no approved treatments for TRAPS. While nonsteroidal anti-inflammatory drugs, corticosteroids and colchicine have been shown to relieve some of the symptoms associated with TRAPS, there can be problems with limited and intermittent efficacy[1,8]. In addition, long-term corticosteroid use in children is associated with potentially serious adverse effects including growth suppression and delayed puberty[8]. Research has also been undertaken into the use of anti-TNF compounds, although none have been approved for use in TRAPS to date.

ACZ885 is a fully human monoclonal antibody that neutralizes IL-1 beta, and could provide a new treatment option, given the potential role of this cytokine in TRAPS. It could also offer a convenient dosing regimen due to its half-life of 28 days.

Key clinical ACZ885 data

There is an ongoing, Phase II, open-label, multicenter study investigating the efficacy and safety of ACZ885 in patients with active TRAPS (ClinicalTrials.gov identifier NCT01242813). The study involves twenty patients with a median age of 39 years (range, 7–78 years). An interim analysis showed that

ACZ885 produced a rapid and highly effective clinical benefit. The safety profile observed in this study was similar to those already seen for ACZ885's approved indication in CAPS[9].

In the Phase II study, 90% of TRAPS patients treated with ACZ885 experienced clinical remission after only one week of starting treatment. Clinical remission included a clinically significant improvement of disease symptoms, as assessed by the treating physician. After two weeks of treatment, 95% of patients with TRAPS treated with ACZ885 had achieved the primary endpoint of a complete or almost complete response. Complete response was defined as clinical remission and normal C-reactive protein (CRP) levels and/or serum amyloid A (SAA) levels, both of which are protein markers of inflammation. Almost complete response was defined as clinical remission and elevated but ≥70% reduction of baseline CRP and/or SAA. Clinical remission was maintained for all patients from Day 15 onwards in the four-month treatment period, except for one patient with a relapse at Day 85 who responded to the scheduled ACZ885 dose[9].

Ninety five percent of patients (n=19) reported at least one adverse event (AE). Infection (mostly upper respiratory tract infection [URI]), was the most common category of AE reported. One serious AE, a URI that lasted two days, was reported[9].

Development of ACZ885 in other areas

ACZ885 is being studied in other diseases in which IL-1 beta plays a prominent role in inflammation, such as systemic juvenile idiopathic arthritis (SJIA), gouty arthritis and cardiovascular disease. Not all patients with these diseases would be eligible for treatment with ACZ885, if approved.

References

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