REGULATORY WATCH

# IL-1β-targeted antibody approved for rare autoinflammatory disorders

In June 2009, canakinumab (Ilaris; Novartis) — a human monoclonal antibody that targets interleukin 1 beta (IL-1β) — was approved by the FDA for the treatment of cryopyrin-associated periodic syndromes (CAPS), specifically familial cold autoinflammatory syndrome (FCAS) and Muckle–Wells syndrome (MWS). This novel agent offers significant advantages over existing therapies, including treatment only every 2 months and approved use in children.

CAPS comprise a group of rare, long-term and potentially life-threatening autoinflammatory disorders of increasing severity: FCAS, MWS and neonatal-onset multisystem inflammatory disease (NOMID). Symptoms can be debilitating and include fatigue, fever, skin rash, inflammation and arthralgia. Until recently, therapeutic options have been limited. "Previous treatments include NSAIDS [non-steroidal anti-inflammatory drugs] and other non-specific anti-inflammatory medicines, such as corticosteroids, that were only partially effective and had several side effects," says Hal Hoffman, University of California, San Diego, USA.

However, there have been some significant recent advances. "Over the last 5 years, increased understanding of the pathogenesis of CAPS based on translational research has established a central role of IL-1β in these diseases," notes Hoffman. Indeed, it is now known that mutations in *NLRP3*, the gene encoding cryopyrin — which controls the processing and secretion of the pro-inflammatory cytokine IL-1β — underlie these disorders, as they result in overproduction of IL-1β.

Dysregulated IL-1β activity, owing to elevated IL-1β levels or a deficiency of the endogenous IL-1β receptor antagonist, is characteristic of autoinflammatory diseases, and several agents targeting IL-1β activity are now in development (Supplementary information S1 (table)). Two of these have previously received FDA approval — the IL-1 receptor antagonist anakinra (Kineret; Amgen/Biovitrum) and the soluble IL-1β decoy receptor rilonacept (Arcalyst; Regeneron) (*Nature Rev. Drug Discov.* **7**, 385–386; 2008). Hoffman explains that, although both of these agents have been successfully used to treat CAPS, they are not without limitations, including the need for frequent injections, as well as their high cost.

The approval of canakinumab follows a 48-week randomized placebo-controlled trial involving 35 children and adults with CAPS (*N. Engl. J. Med.* **360**, 2416–2425; 2009). Canakinumab was reported to produce a rapid (within hours), complete and sustained response in most patients, and was well tolerated without any consistent pattern of side effects. Importantly, canakinumab exhibited several advantages over existing therapies. "Canakinumab is a potent IL-1β blocker with excellent efficacy for CAPS comparable to other available IL-1β therapies, with the advantages of approval in children down to 4 years old, a dosing schedule of just every two months and less injection site reactions," notes Hoffman.

Clinical trials of canakinumab are also underway in NOMID, as well as other disorders (Supplementary information S1 (table)). "This is a great advance for the study of IL-1β in inflammatory diseases, and is just the beginning," notes Charles Dinarello, University of Colorado School of Medicine, Denver, USA. "In addition to the rare CAPS and similar auto-inflammatory diseases, the enormous population of patients with type 2 diabetes and smoldering myeloma could also benefit greatly from treatment with IL-1β monoclonal antibodies. Xoma-052 [another such antibody] appears to protect the insulin-producing beta cells in the pancreatic islet and promises to be an important step in arresting inflammation in type 2 diabetes; and, in patients with smoldering myeloma, IL-1β blockade has prevented the progression to full-blown multiple myeloma for years compared with months for historical controls," adds Dinarello. "Other possible uses for agents that reduce IL-1β activity are in acute stroke, gout, myocardial infarction with ventricular remodelling, and osteoarthritis," Dinarello proposes.