Commentary: “Preclinical Characterization and Clinical Development of ILARIS (Canakinumab) for the Treatment of Autoinflammatory Diseases”

Hermann Gram*

Novartis Institutes of BioMedical Research, Forum 1, CH-4002 Basel, Switzerland

IL-1β is an ancient cytokine found in the entire vertebrate lineage. It is part of the innate response towards infections, and in mammals it is essential part of the fever response. IL-1β has been recognized or proposed as pathogenic factor causing or contributing to numerous of diseases, clinical conditions, or syndromes. It is not surprising that more than two decades ago pharmaceutical research towards the inhibition of IL-1β started. Three marketed drugs resulted from these endeavors: Anakinra, a recombinant form of the endogenous IL-1 receptor antagonist, was approved first by the FDA in 2001 for the treatment of rheumatoid arthritis; Rilonacept, a recombinant soluble IL-1 receptor, achieved market authorization for Cryopyrin Associated Periodic Syndrome (CAPS) in 2008; and Canakinumab, a monoclonal antibody targeting IL-1β, obtained its first market authorization for CAPS in 2009. It is surprising that despite ample evidence for a pathogenic role of IL-1β in a large number of preclinical animal studies this research resulted in relatively few successful development programs and marketed clinical indications. Such approved indications are CAPS (Anakinra, Rilonacept, Canakinumab), rheumatoid arthritis (Anakinra), systemic juvenile idiopathic arthritis (sJIA, Canakinumab) and refractory gout (Canakinumab). The reasons for this discrepancy may lie in the translation of mechanistic animal models to complex human diseases. Indeed, IL-1 blockers failed to show a clinically relevant benefit over placebo or standard of care in a number of clinical trials, e.g., in sepsis, osteoarthritis, or COPD. However, IL-1 targeting drugs have shown unprecedented efficacy in rare autoinflammatory diseases. Amongst those, CAPS can be considered as the prototypic disease which is intimately linked to a dysfunctional regulation of IL-1β production. CAPS is a rare disease with an incidence of about 1-2 cases per million, and mostly caused by mutations in the NLRP3 gene which leads to activation of the inflammasome, a multi-protein complex directly controlling the secretion of active IL-1β from cells. CAPS patients are characterized by overproduction of IL-1β by their lymphocytes, and by recurrent fevers, rash, arthralgia, progressive hearing loss and amyloidosis in some cases.

Canakinumab is a human monoclonal antibody potently and specifically neutralizing the activity of human IL-1β. This antibody was derived from hybridomas generated from genetically engineered mice carrying part of the human immunoglobulin genes.
Biochemical and structural analysis revealed that glutamine 64 in human IL-1β is a key residue for the interaction with Canakinumab. This residue is rarely conserved in mammalian species, explaining the narrow species crossreactivity only to marmoset, a small non-human primate species suitable for toxicological assessments. Canakinumab is the only approved drug which specifically targets IL-1β, but not IL-1α or IL-1Ra.

The first full clinical development of Canakinumab was performed in CAPS, where it induced a long-term clinical remission and normalization of C-reactive protein, a marker of systemic inflammation. Clinical relapse and recurrence of symptoms occurred after several months in patients treated with a single injection of Canakinumab. Time to relapse was related to the dose, and clinical remission could be restored upon re-treatment with Canakinumab. A pivotal phase III clinical trial using a withdrawal design was conceived based on the observation of the clinical relapse pattern in seven patients treated with Canakinumab. A combination of the relapse pattern with a pharmacokinetic/pharmacodynamic (PK/PD) model predicted the probability of a clinical relapse within a given time for a given dose of Canakinumab. The model derived proposal for a dosing scheme of a subcutaneous injection of 150 mg of Canakinumab every two months was confirmed in a phase III study, resulting in lasting suppression of clinical symptoms. As CAPS represents a wide spectrum of clinical manifestations, dose adjustments up to 300 mg/month might be required for severe or very young patients to achieve full clinical and sustained efficacy. The main side effect reported for Canakinumab is an increased risk of serious infections, which is common to all medications currently studied in a large cardiovascular outcome trial to test the hypothesis that neutralization of IL-1β specifically reduces the risk of a secondary cardiovascular event in patients with a previous myocardial infarction. Also, blockade of IL-1 by anakinra provided initial evidence of a potential clinical benefit on heart function in small studies with heart failure patients displaying an increased inflammatory burden. Further, IL-1β may have a major role in ischemia/reperfusion induced small vessel occlusion, leucocyte extravasation and endothelial activation, which is a major clinical problem in sickle cell anemia. Indeed, IL-1β neutralization in a mouse model of sickle cell disease provided a significant improvement in vessel occlusion, granulocyte extravasation and hemodynamics. It remains to be seen whether these predicted benefits can be verified in clinical studies.

In summary, specific IL-1β blockade by Canakinumab has shown excellent efficacy and a favorable benefit vs. risk profile in a number of rare autoinflammatory syndromes, and there is evidence that IL-1β may play a significant role in pathological changes in myocardial and vascular endothelium. Due to its exclusive specificity for IL-1β, Canakinumab is an excellent pharmaceutical tool to address the pathophysiological role of IL-1β and the utility of IL-1β neutralization in disease.
References


10. Touitou I. International Society for Systemic AutoInflammatory Diseases [InFevers] [Internet]. Available at : http://www.aiims.org/issaid/infevers/index.php; accessed June 1st, 2016.


