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

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IL-1β is an ancient cytokine found in the entire vertebrate lineage[1]. It is part of the innate response towards infections, and in mammals it is essential part of the fever response[2]. IL-1β has been recognized or proposed as pathogenic factor causing or contributing to numerous of diseases, clinical conditions, or syndromes[3,4]. 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[5-7]. However, IL-1 targeting drugs have shown unprecedented efficacy in rare autoinflammatory diseases[8,9]. 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[10].

Canakinumab is a human monoclonal antibody potently and specifically neutralizing the activity of human IL-1β[11]. 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[12]. 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[13]. 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[14]. The main side effect reported for Canakinumab is an increased risk of serious infections, which is common to all medications targeting IL-1β[15].

A growing list of autoinflammatory syndromes has been identified which are associated with specific genetic defects[16]. Many of these identified syndromes, mostly characterized by fever attacks of variable length, respond to some extent to IL-1β blockade, but systematic studies were lacking for most of these syndromes. Most of the evidence for a clinical benefit by IL-1 targeting was generated in open label studies for Familial Mediterranean Fever (FMF), TNF Receptor Associated Periodic Syndrome (TRAPS) and Hyper IgD Syndrome/Mevalonate Kinase Deficiency (MKD/HIDS). Interestingly, the respective genetic defects in these diseases affect cellular pathways and molecules which are not directly upstream of IL-1β, but their physiological consequences appear to converge on the overproduction of IL-1β. Indeed, Canakinumab had shown highly encouraging results in small open label clinical studies in these autoinflammatory syndromes. Canakinumab is the first IL-1β targeted therapy in a controlled phase III study which enrolled FMF, TRAPS, and MKD/HIDS patients under a combined protocol. Excellent efficacy was observed in all three sub-studies, and first results have just been reported at the EULAR meeting in June this year[17]. Respective applications for market authorization in these three autoinflammatory diseases are currently pending.

Genetic diagnosis of an autoinflammatory syndromes will aid today a physician's decision for treatment with an IL-1 targeted therapy, however, there are autoinflammatory syndromes without a clear cut genetic cause, but characterized by spiking fever and leukocytosis, e.g., sJIA or Schnitzler's syndrome, which both show excellent response to neutralization of IL-1β[18,19,20], suggesting that clinical hallmarks indicative of IL-1 dependent autoinflammation can predict the successful use of an IL-1 targeting agent. However, such a therapeutic approach on autoinflammatory syndromes of unknown etiology requires a comprehensive diagnostic workup, exclusion of opportunistic infections or malignancies, and preferably, demonstration of IL-1β overproduction by peripheral blood mononuclear cells in vitro prior to a treatment decision.

While fever is indicative of high systemic IL-1β activity in autoinflammation, IL-1β may play a pivotal role in endothelial dysfunction which is accompanied by subclinical inflammation. Atherosclerosis has been recognized as an inflammatory disease in which IL-1β is postulated to have a pathogenic role by different mechanisms[21]. Notably, the inflammasome can be activated in the atherosclerotic plaque by deposits of cholesterol crystals, leading to the induction of IL-1β which is believed to favor plaque instability and rupture. Canakinumab is 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[22]. 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[23,24]. 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[25]. Indeed, IL-1β neutralization in a mouse model of sickle cell disease provided a significant improvement in vessel occlusion, granulocyte extravasation and hemodynamics[26]. 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.

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