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Commentary

IL-1 inhibitors: What is their right position as therapeutic opportunity?

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Ever since the first description of Interleukin-1 (IL-1), there has been great interest in understanding how it and its related cytokines play such a key role in inflammatory responses. The large IL-1 family has 11 members with anti-inflammatory activity: seven pro-inflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, and IL-36α, β and γ) and four antagonists (IL-1 receptor [IL-1R] antagonist [IL-1RA], IL- 36RA, IL-37, and IL-38), of which IL-1α and IL-1β are the most widely studied.

The IL-1 family plays a key pathogenic role in auto-inflammatory, auto-immune, infectious, degenerative and malignant diseases, and the subsequently acquired knowledge has led to the development of specific strategies for inhibiting some of its members. Nevertheless, it is surprising how much more has been discovered about its role inflammatory processes over the last 20 years [1-4].

It is now known that many auto-inflammatory and auto-immune diseases are characterised by a multifaceted network of dynamic interactions between innate and adaptive immunity, although the boundary between these two characteristics is becoming blurred as a result of the increasing number of diseases reported to be characterised by both. The crucial role of the multifunctional IL-1 family has understandably increased interest in the possibility of targeting these cytokines in the treatment of a wide range of auto-inflammatory diseases, including Rheumatoid Arthritis (RA), gout, cardio metabolic diseases (including Type 2 Diabetes [T2D], atherosclerosis and malignancies [5,6], the natural course of many of which has been radically changed by blocking or reducing IL-1 activity [7-10].

Only two of the four currently available IL-1 inhibitors have been approved for use in Europe: the receptor antagonist anakinra (ANA) and the selective IL-1β inhibitor canakinumab (CAN). ANA binding the IL-1 receptor type I inhibit both the IL-1 subunits a and β.

After it had been proved to be capable of reducing joint destruction, ANA was approved in 2001 for the treatment of moderate-severe RA in association with methotrexate. However, it is only infrequently used in patients with early and established RA because it is less efficacious than the currently dominant TNF inhibitors and other biological agents [11-13]. ANA has also been found to be effective in many other joint and muscular diseases, and its other currently approved indications are Cryopyrin-Associated Periodic Syndromes (CAPS) and Adult-Onset Still's Disease (AOSD) [14].

Several clinical trials about its efficacy on decreasing cardiovascular risk and cardiovascular events have also been developed after that animal experiments have confirmed its cardiovascular effectiveness [15]. Five clinical trials have shown that the most frequent ANA-related adverse events are injection site reactions, infections (at doses of >100 mg), and immunogenicity. Furthermore, as it has a short half-life of 4-6 hours, ANA must be injected every day and is therefore often poorly tolerated.

CAN is a human monoclonal antibody with a high affinity for human IL-1β, is mainly eliminated by means of intracellular catabolism, and has a half-life of 26 days. Its binding to circulating IL-1β blocks the interaction between IL-1β to its receptor neutralizing its activity. Its high affinity and specificity for IL-1β makes it very suitable for various therapeutic purposes [16,17], and its bi-weekly administration gives it a great advantage over ANA. Originally approved for the treatment of CAPS in 2009, its rapidly increasing indications now include Tumour necrosis factor Receptor-Associated Periodic Syndrome (TRAPS), hyperimmunoglobulinemia D syndrome/mevalonate kinase deficiency (HIDS/MKD), Familial Mediterranean Fever (FMF), gout, Systemic Juvenile Idiopatic Arthritis (SJIA), and AOSD, in all of which it leads to a rapid and sustained improvement in symptoms, a complete clinical response, and a reduction in inflammatory markers (serum C-reactive protein and amyloid-A). It also has a good safety profile. Long-term remission has been observed in patients with SJIA.

There is ample evidence showing that anti-IL-1

agents have a strong steroid-sparing effect, and lead to a reduction or discontinuation of disease-modifying anti-rheumatic drugs, accompanied by a significant decrease in the side effects of co-treatments [18]. These effects have been confirmed in patients with AOSD, in whom high response rates have been consistently reported (especially in refractory cases), with complete or partial remissions in most, a reduction or discontinuation of steroids, and decreased co-treatment side effects. However, joint symptoms are less well controlled than systemic symptoms, and can take longer to respond to treatment. The efficacy of anti-IL-1 agents suggests that early treatment can avoid serious disease- or co-treatment-related complications, and new findings continue to reveal novel indications [19].

Recent extensive research has demonstrated that IL-1 may be at the centre of hypotheses linking inflammation with the pathogenesis of atherosclerosis, and may be involved in pathological cardiac events after a myocardial infarction, including the inflammation and remodelling that weaken heart muscle tissue and contribute to subsequent heart failure [20]. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) confirmed that IL-1 (particularly IL-1β)-related inflammation is an independent risk factor for cardiovascular events [20]. The primary endpoint of the CANTOS was the incidence of adverse cardiac events (cardiovascular death, myocardial infarction, or stroke), and the results showed that CAN was superior to placebo in preventing them.

It has been found that IL-1α and IL-1β are over-expressed in patients with advanced neoplasms, and that this was associated with higher tumour grades and greater invasiveness [21]. Pre-clinical studies of ANA have reported inhibited colon tumour growth, a significant survival benefit, and improved quality of life scores when it is added to standard-of-care chemotherapy in patients with metastatic colorectal cancer [22], and one unexpected finding of CANTOS was a significantly lower incidence of lung cancer and deaths due to all cancers in CAN-treated patients [23]. This latter finding inspired several trials such as one of combination with canakinumab and a programmed cell death protein 1 (PD-1) inhibitor in patients with non-small cell lung cancer [24,25]. However, further studies are required to clarify the possible role of IL-1 inhibition in the treatment of cancer.

Anti-IL-1 therapy may have a beneficial effect on T2D as it has been found that it improves insulin production and glycemic control, and decreases C-Reactive Protein (CRP) and IL-6 levels [26]. Its possible protective role in type 1 diabetes has also been evaluated.

Other studies have tested CAN and ANA in patients with chronic obstructive pulmonary disease, sarcoidosis, Behçet's disease, pyoderma gangrenosum, Schnitzler's syndrome and urticarial vasculitis with encouraging results, and it is likely that the indications for CAN will be further extended.

A number of genetic modifications and mutations associated with dysregulated IL-1 activity and auto-inflammatory manifestations have been identified in humans and animal models, and IL-1 inhibitors have been found to be effective in diseases that were previously considered untreatable. The identification of auto-inflammatory disorders associated with increased levels of other cytokines in the IL-1 family should also permit the development of specific anti-cytokine therapies.

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