JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES, 2018
VOL. 8, NO. 1, 21–22
https://doi.org/10.1080/20009666.2018.1428023

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PERSPECTIVE

Canakinumab and cardiovascular outcomes: results of the CANTOS trial

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ABSTRACT

IL-1 cytokines are mainly responsible for controlling a series of pro-inflammatory reactions induced in response to pathogen mediated tissue injury. Among the IL-1 cytokine family, IL-1 β results in upregulation of genes responsible for boosting immune system reactivity and inflammatory response. With growing pathophysiological relevance of IL-1β in a myriad of disease pathogenesis, new biological drugs have been developed in recent years. One such drug, Canakinumab, targeting IL-1β has been recently approved for clinical use. The recent results from the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial are encouraging in this aspect. The results suggest that anti-inflammatory therapy using canakinumab at a dose of 150 mg every 3 months led to significantly lower recurrent cardiovascular events than the placebo drug. These results were independent of lipid-lowering effects of these drugs. If the results are widely applicable, the CANTOS trial would reaffirm the hypothesis of atherothrombosis due to inflammation, hence supporting the need for a cytokine-based therapy for the secondary prevention of cardiovascular diseases. Moreover, the potential benefits of the phenomenal reduction in the inflammatory cascade induced by canakinumab should be carefully balanced against its long-term safety profile which is yet unknown. However, the inflammatory hypothesis of atherothrombosis supports a cytokine-based therapy for the secondary prevention of cardiovascular disease. Furthermore, the potential benefits from the reduction in inflammatory markers induced by canakinumab should be carefully balanced against its unknown long-term safety profile.

ARTICLE HISTORY
Received 29 October 2017
Accepted 5 January 2018

KEYWORDS
CANTOS; Canakinumab; cardiovascular; mortality; antiinflammatory

The ligands and receptors belonging to the IL-1 family are primarily associated with both acute and chronic inflammation [1]. IL-1 type cytokines, including both IL-1α and IL-1β, mainly control the pro-inflammatory reactions in response to pathogen-induced tissue injury [1]. The major sources of the secreted IL-1α and IL-1β are the cells of the innate immune system [1]. Between the two, IL-1β is secreted as an inactive precursor which is transformed into its active mature form with the help of Caspase 1 enzyme. Upon maturation, IL-1β is released in the extracellular fluid and binds to the receptor (IL-1R). This ligand–receptor interaction leads to IL-1 signal transduction, subsequently leading to an upregulation of genes, resulting in an enhanced immune system reactivity and inflammation [1].

With the growing pathophysiological relevance of IL-1β being involved in the pathogenesis of a wide variety of diseases, new biologic drugs have been introduced to restrict the actions of these inflammatory cytokines in recent years. Canakinumab is one such IL-1β targeting drug which has been approved for clinical use. This human IgG1k monoclonal antibody neutralizes soluble IL-1β. It is a human IgG1k monoclonal antibody that neutralizes soluble IL-1β. Initially, Canakinumab was approved for treating Cryopyrin-Associated Periodic Syndromes and other inflammatory disorders including Stills disease, gout, and Behçets syndrome [2–6]. With passing time, active vaccines against endogenous inflammatory cytokines were introduced as a novel approach to block the actions of IL-1β [7]. Coupled with virus-like particles, the vaccine hIL1bQb was proven to produce anti-IL-1β antibodies endogenously in preclinical models. Currently, these vaccines are being tested in the clinical setting [8].

Recently, monoclonal antibodies to IL-1β have been successful in controlling inflammatory markers. In addition to their approved indications so far, these drugs are currently being tested and used in preclinical and clinical trials to assess their widespread applicability and relevance in other pathological conditions in which IL-1β has a key role to play. These very trials led to additional investigation into exploring the role of canakinumab in suppressing the effects of inflammatory markers. One such trial was the CANTOS

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(Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial where promising results were seen [9]. During the trial, 10,061 patients with previously diagnosed myocardial infarction were targeted [9]. Three doses of canakinumab (50, 150, and 300 mg, administered subcutaneously every 3 months) in addition to a placebo were compared with the primary efficacy point being nonfatal myocardial infarction or cardiovascular death. Inflammatory markers including high-sensitivity C-reactive protein level was measured during the study. At 4 years, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26, 37, and 41 percentage points greater in the group than in the placebo group that received 50-, 150- and 300-mg, respectively. Furthermore, the incidence rate for primary end point was 4.50 events per 100 person-years in the placebo group as compared to 4.11, 3.86, and 3.90 in the 50-, 150- and the 300-mg group, respectively [9]. The results with the 150-mg dose, but not with the other doses, met the statistical significance for the primary end point. However, no significant difference was noted in all-cause mortality [9].

The results of this trial suggested that anti-inflammatory therapy with canakinumab at a dose of 150 mg every 3 months leads to significantly lower chances of recurrent cardiovascular events than the placebo, independent of lipid-lowering effect, serving as a landmark in the history of cardiovascular disease management. If the results are widely applicable, the CANTOS trial reinforces the hypothesis of inflammation being the cause of atherothrombosis and will reaffirm the need of a cytokine-based therapy for the secondary prevention of cardiovascular events [10,11,12].

However, there were some adverse side effects of canakinumab in the trial which need to be addressed: patients receiving canakinumab were more prone to having infections due to neutropenia and had significantly more deaths as compared to the placebo group owing to infection or sepsis [9]. However, the all-cause mortality rate was insignificant between the canakinumab and placebo groups [9].

Despite the cardiovascular benefit, a few limitations are yet to be addressed to assess the structural changes, like the short duration of the study, sample size, dosage, and the enrollment of patients with preexisting advanced stage cardiovascular disease. Thus, parallel studies involving patients with no evidence of advanced cardiovascular disease would help shed light on the capacity of canakinumab in the prevention or slowing down of the onset of atherothrombosis or other vascular changes.

The increasing evidence reiterating IL-1β as a predominant player in the development of cardiovascular insults provides a sound rationale for the need for IL-1 blockade as a possible pharmacological strategy to treat and manage the disease. With forthcoming trials resembling the CANTOS trial, further novel pharmacological approaches such as therapeutic vaccination should be explored, allowing us to answer whether IL-1β is indeed a valuable target for establishing a therapeutic benefit in addition to reducing the burden of cardiovascular complications. The phenomenal reduction in inflammatory markers due to canakinumab should be carefully assessed against its unknown long-term safety profile. Soon, implementation of the results of the CANTOS trial is anticipated in international guidelines.

Disclosure statement

No potential conflict of interest was reported by the author.

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