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A Promising Treatment for Osteoarthritis?

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Osteoarthritis, the most common type of arthritis, increases in prevalence with age and is a leading cause of joint pain and disability worldwide (1). Currently, no treatments exist that can either prevent or slow progression of the disease. Osteoarthritis is characterized by loss of articular cartilage, bone remodeling, and synovial inflammation. Studies suggest that both inflammation and abnormal joint loading trigger local release of inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor. These inflammatory cytokines alter the chromatin landscape and activate the genes that transcribe proteins catabolic to cartilage and bone, including matrix metalloproteinases, ADAMTS5, and MAP kinases. Also, inflammatory cytokines can induce other disease-related genes within the inflamed synovium, including nerve growth factor and prostaglandin E2, key pain sensitizers in osteoarthritis (2).

The role of systemic inflammation in osteoarthritis has been a topic of great interest. The relation of these inflammatory mediators to risk for osteoarthritis may identify patients who would benefit from specific therapies. One such biomarker, C-reactive protein (CRP), reflects systemic and localized inflammation and is induced by inflammatory cytokines in the liver, in inflammatory cells within the synovium, and at other sites of inflammation. High-sensitivity CRP (hs-CRP) is associated with an increased risk for painful osteoarthritis (3, 4). However, the precise role of CRP in osteoarthritis development is unclear. Because CRP production is activated by inflammatory cytokines, including IL-6 and IL-1β, the serum level of CRP also may reflect inflammation within the joint.

Trials testing IL-1 inhibitors for knee osteoarthritis (Table) have ranged from 4 to 50 weeks in duration and have tested monoclonal antibodies that block IL-1 activity by interfering with either IL-1 or its receptor. All the trials focused on pain outcomes, and although none showed a significant reduction in pain in patients randomly assigned to IL-1 inhibition versus the placebo groups, results in the non-canakinumab studies trended toward modest efficacy, with an average 5% to 10% lower pain score in the active-treatment versus the

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placebo groups. No studies tested the effect of an IL-1 inhibitor on radiographic disease progression or cartilage loss. Trials testing inhibitors of tumor necrosis factor-α, another inflammatory cytokine, have also been null–although, like the IL-1 studies, most have shown small, nonsignificant reductions in pain for patients receiving active treatment versus those receiving placebo.

CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) was a trial that tested IL-1 inhibition as a treatment for secondary prevention of cardiovascular disease. It included 10 061 patients with a history of myocardial infarction and an hs-CRP level of 2 mg/L or greater. The trial compared 3 doses (50, 150, and 300 mg) of canakinumab–a monoclonal antibody targeting IL-1β–and placebo, administered subcutaneously every 3 months for up to 5 years. Patients who received canakinumab had a significantly lower rate of recurrent cardiovascular events and related mortality than those in the placebo group (9). However, patients in the canakinumab groups also had a greater number of serious infections and higher infection-related mortality, which canceled out any overall reduction in mortality; therefore, canakinumab was not recommended for secondary prevention of cardiovascular disease.

As part of CANTOS, data were collected on all adverse events (AEs). Because total hip or total knee replacement (THR/TKR) requires hospitalization and all hospitalized events are reported as serious AEs in a trial, a comprehensive count of THR/TKRs exists. More than 90% of replacements were performed for osteoarthritis. Joint pains and other potential osteoarthritis symptoms were queried as AEs, but information on these outcomes was nonspecific and likely inconsistently collected.

In their report for *Annals*, Schieker and colleagues (10) present a secondary analysis of osteoarthritis data from the CANTOS trial. The primary end point was time to first THR/TKR, with a median follow-up of 3.7 years. The combined incidence rates for THR/TKR were 40% to 47% lower with canakinumab treatment; the hazard ratios were 0.54 (95% CI, 0.36 to 0.81) among men and 0.66 (CI, 0.38 to 1.12) among women. All canakinumab doses reduced the number of joint replacements similarly. The reduction in joint replacements among patients who received canakinumab versus the placebo group became apparent after only 1 year of treatment. The effects of canakinumab remained statistically significant when CANTOS participants with a history of crystalline or inflammatory arthritis were excluded. However, the number of women in this trial was low, which is a concern given that knee osteoarthritis is a disease that predominates in older women.

The results of this exploratory trial are both unexpected and exciting, and novel aspects of the trial design deserve comment. The investigators used elevated hs-CRP level as an entry criterion. This requirement, not routine in osteoarthritis trials, may have identified a subgroup of persons with osteoarthritis in whom inflammatory cytokines activate pathways that accelerate joint degeneration.

Most osteoarthritis trials, even those focusing on radiographic osteoarthritis progression, are of much shorter duration than this study. The primary study end point was time to joint replacement. Total hip or total knee replacement is performed in patients who

have unacceptably high levels of joint pain or functional impairment despite medical and rehabilitative treatment, and they usually have advanced radiographic deterioration in the affected joint. Joint replacement is a robust end point and one that might be adapted by the U.S. Food and Drug Administration for evaluating disease-modifying osteoarthritis drugs.

On the basis of our understanding of osteoarthritis pathophysiology, IL-1 is a central player in both cartilage degradation and the enhancement of joint pain. This secondary analysis of the CANTOS trial presents intriguing results that may offer promise for IL-1 inhibition as a treatment. Further studies should evaluate the importance of elevated CRP levels as a factor affecting response to treatment, include more women to better reflect the osteoarthritis population, explore how to minimize infections, and try to better define the duration of therapy needed to detect treatment effects. This unexpected finding deserves additional investigation in developing potential disease-modifying osteoarthritis drugs.

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Table.

Randomized Placebo-Controlled Trials of IL-1 Inhibitors for Knee Osteoarthritis

Study, Year (Reference)	IL-1 Treatment	Patients, *n*	Outcome	Duration, *wk*	Results
Chevalier et al, 2009 (5)	Anakinra (IL-1RA)*	170	Pain	4	Null
Fleischmann et al, 2019 (6)	Antibody to IL-1α/β	350	Pain/synovitis	50	Null for both outcomes
Cohen et al, 2011 (7)	mAb to IL-1R1	160	Pain	12	Null
NCT01160822 (8)	Canakinumab (mAb to IL-1β)*	136	Pain	4	Null

IL-1 = interleukin-1; IL-1R1 = IL-1 receptor, type 1; IL-1RA = IL-1 receptor antagonist; mAb = monoclonal antibody.

*Intra-articular administration of treatment and placebo.