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REVIEW

Desperately looking for the right target in osteoarthritis: the anti-IL-1 strategy

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Abstract

Blocking IL-1 in patients with knee osteoarthritis is an attractive strategy. Cohen and colleagues report a randomised, placebo-controlled, multiple-dose trial using a monoclonal antibody blocking IL-1 type 1 receptor. They failed to show any positive results in terms of evolution of pain for up to 12 weeks, in line with the former trials using intraarticular injections of IL-1 receptor antagonist. A trend was observed, however, in a subgroup of patients with high level of pain at baseline. Although these data may suggest cessation of IL-1 therapy in osteoarthritis, other methods such as limited intraarticular anti-IL-1 delivery should still be considered.

One of the most exciting challenges in rheumatology for the future is to find a therapeutic target for osteoarthritis (OA) [1]. Indeed, clinicians and our patients are still waiting for a new drug that exhibits an analgesic effect and structure-modulating properties.

OA is characterised by an imbalance between catabolic and anabolic responses of stimulated chondrocytes, driven locally by a soup of cytokines where IL-1β is regarded as the chief orchestrator. On the one hand, IL-1 can induce the production of enzymes, prostanoids, nitric oxide and free radicals; on the other hand, IL-1 can block the production of collagen type 2 and proteoglycans [2,3]. IL-1 is also involved in the transmission of pain [4]. Considering all these factors, targeting IL-1 in OA seems a logical approach to slow down the disease progression.

In different animal models, Martel-Pelletier and colleagues were the first to use IL-1 receptor antagonist (IL-1ra) injected intraarticularly – either directly or through gene therapy – with encouraging results in terms of cartilage preservation [5]. Moreover, in patients with rheumatoid arthritis, anakinra (IL-1ra) injected subcutaneously daily demonstrates a disease-modifying antirheumatic effect [6].

In this context, we performed two trials with one single intraarticular injection of IL-1ra in knee OA [7,8]. The main result of the randomised, placebo-controlled trial using two doses of IL-1ra (50 mg and 150 mg) was negative regarding the evolution of pain after a follow-up of 3 months [8]. However, different hypotheses could possibly explain this negative result: the short half-life of IL-1ra, the single intraarticular injection, or the excess of IL-1ra already present in the synovial fluid.

The contribution of Cohen and colleagues, published in the present issue of *Arthritis Research & Therapy*, is therefore a major contribution to enlighten the anti-IL-1 strategy in OA [1]. The authors use systemic administration of a monoclonal antibody (AMG 108) directed against the functional type 1 receptor of IL-1. This is a two-part randomised, double-blind, placebo-controlled, multiple-dose study in patients with OA. The most interesting part of the study is the second, in which patients received 300 mg AMG 108 subcutaneously once every 4 or 12 weeks compared with placebo. There are two major conclusions that could be drawn from this study: one on efficacy, and one on safety. The main endpoint was the level of pain at 6 weeks and no statistical difference with placebo was observed. Furthermore, AMG 108 induced a decrease in neutrophil count and, while the incidence of serious infections was similar in the AMG 108 and placebo groups, a death in this trial might be indirectly related to neutropaenia in an 80-year-old man and may lead to suspension of the programme.

Regarding this negative trial, should we definitively put nails in the coffin of an anti-IL-1 option in OA?

Looking at the benefit/risk ratio in the study by Cohen and colleagues, it is tempting to answer yes. However, we should probably bring some reservations to this opinion.

First, there is a real trend of efficacy favouring AMG 108 compared with placebo, especially in patients with a high level of pain at baseline (Western Ontario and

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MacMaster Universities index >325). Lack of difference may be linked to the small number of patients in this subgroup (n = 22 AMG 108-treated patients and n = 25 placebo-treated patients), which may subsequently contribute to the overall negative result. Similarly, significant efficacy was observed in the randomised, placebo-controlled trial with one single intraarticular injection of IL-1ra (150 mg) compared with placebo at day 4, suggesting some real but unstained clinical benefit [8]. Interestingly, ultrasensitive C-reactive protein levels decreased with anti-IL-1 therapy [1]. C-reactive protein is a relevant marker in OA related to tibial cartilage volume and local inflammation, and is a good prognostic marker of disease progression [9,10]. The question of chondroprotection by anti-IL-1 therapy is still so far unanswered, although some preliminary results with magnetic resonance imaging indicate improvement of synovial membrane inflammation [8]. The nonlinear nature of the pharmacokinetics may also contribute to variations in the local concentration of AMG 108 in the synovial fluid (calculated to be around 50 nM) [1]. The remaining question is whether this concentration is able to block IL-1 activity not only in the synovial fluid but also in the superficial cartilage layers.

The other conclusion concerns safety. What we can learn from this current study is that long-term biotherapy, which may expose patients to serious side effects, is not acceptable in a benign disease such as OA.

We should therefore rethink an IL-1 strategy in OA. One of the most appealing approaches could be the intraarticular route of administration with repeated intraarticular injections to increase the local concentration of the drug into the joint, especially during flare-up of the disease. In doing so, we can also hope to diminish the risk of serious side effects.

For sure, the story is not finished.

Abbreviations

IL, interleukin; IL-1ra, IL-1 receptor antagonist; OA, osteoarthritis.

Competing interests

The authors declare that they have no competing interests.

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