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...
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 in osteoarthritis of the knee. In doing so, we can also hope to diminish the risk of serious side effects.

For sure, the story is not finished.

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References
1. Cohen SB, Proudmian S, Kivitz AJ, Burch FX, Donohue JP, Burstein D, Sun Y-N, Barfield C, Vincent MS, Ni L, Zack DJ: A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL 1R1) in patients with osteoarthritis of the knee. Arthritis Res Ther 2011, 13:R125.
2. Pelletier JP, Martel-Pelletier J, Abramson SE. Review: osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001, 44:1237-1247.
3. Chevalier X. Up-regulation of enzymatic activity by interleukin-1 in osteoarthritis. Biomed Pharmacother 1997, 51:58-62.
4. Sachs D, Cunha FQ, Poole S, Ferreira SH: Tumour necrosis factor-α, interleukin-1β and interleukin-8 induce persistent mechanical nociceptor hypersensitivity. Pain 2002, 96:89-97.
5. Caron JP, Fernandes JC, Martel-Pelletier J, Tarid G,Mineau F, Geng C, Pelletier JP: Chondroprotective effect of intra-articular injections of interleukin-1 receptor antagonist in experimental osteoarthritis. Suppression of collagenase-1 expression. Arthritis Rheum 1996, 39:1535-1544.
6. Bresnihan B: Anakinra as a new therapeutic option in rheumatoid arthritis: clinical results and perspectives. Clin Exp Rheumatol 2002, 20(Suppl 27):S32-S34.
7. Chevalier X, Giradeau B, Conrozier T, Marillere J, Kiefer P, Goupille P: Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. J Rheumatol 2005, 32:1317-1323.
8. Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, Loeuille D, Kivitz AJ, Silver D, Appleton BE: Intra-articular injection of anakinra (r-met-huIL-1ra) in osteoarthritides of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2009, 61:344-352.
9. Hanna FS, Bell RJ, Cicuttini FM, Davison SL, Wluka AE, Davis SR: High sensitivity C reactive protein is associated with lower tibial cartilage volume but not lower patella cartilage volume in healthy women at mid-life. Arthritis Res Ther 2008, 10:R27.
10. Sharif M, Shepstone L, Elson CJ, Doggre PA, Kinwan JR: Increased serum C reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee. Ann Rheum Dis 2000, 59:71-74.

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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