Are biologics a treatment option in osteoarthritis?

This article examines biologics as emerging therapies for osteoarthritis. There are currently no disease-modifying antiosteoarthritis drugs. IL-1β and TNF-α are two major cytokines produced by the synovial cells and the chondrocytes that are involved in cartilage matrix destruction. Inhibition of these two proinflammatory cytokines appears logical in osteoarthritis (OA). There is sound evidence based on *in vivo* animal models of OA, to support the use of cytokine inhibitors in human clinical trials. The route of administration would preferentially be intra-articular for large joints, such as the knee, and systemic for polyarticular OA, such as hand OA. Two randomized placebo-controlled trials in knee OA, one using intra-articular injection of the antagonist of IL-1 and another using systemic administration of an antibody against IL-1, were negative. Results with TNF-α blockers in hand OA are promising. Biologics will probably be introduced into the treatment armamentarium for OA. However, first, we need to demonstrate their efficacy and then better define to which patient and when biologics should be administered during the course of the disease.

KEYWORDS: cartilage ■ cytokine ■ gene therapy ■ IL-1 ■ inhibitors of cytokines ■ intra-articular administration ■ TNF-α

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Osteoarthritis (OA) is the most common form of arthritis, affecting millions of people in western countries [1]. Although the hallmark of the disease is progressive degeneration of the articular cartilage, which causes narrowing of the joint space, OA also causes pain, loss of motion, instability and physical disability, thus impairing quality of life.

The development of new treatments for OA is constrained by the slow progression of the disease, heterogeneous clinical manifestations and need for long-term follow-up to detect structural changes. There are currently no disease-modifying anti-OA drugs. Guidelines for optimal OA management, particularly for hip, knee and hand OA, must rely on a combination of nonpharmacological and pharmacological modalities [2,3]. Pharmacological interventions consist primarily of the prescription of analgesics (chiefly acetaminophen and nonsteroidal anti-inflammatory drugs), intra-articular injections of corticosteroids and/or hyaluronic acid, and chondroprotective drugs, known as symptomatic slow-acting drugs for OA [2,3]. However, symptomatic slow-acting drugs for OA have only modest disease-modifying effects in knee and hip OA [2]. Patients who do not obtain adequate pain relief and functional improvement from a combination of these modalities should be considered for joint replacement surgery.

The optimal treatment for OA would be a drug or combination of drugs capable of substantially decreasing disease progression, such as those now available for rheumatoid arthritis (RA). The challenge is to identify targets for such drugs. Another big challenge in the future will be to identify patients with early OA in order to start the treatment before irreversible damage of the cartilage matrix occurs.

Pathophysiology

The exact etiology of OA is unknown. Recently, advances have been made in understanding the pathophysiology of OA. Accumulating evidence indicates a role for both systemic factors and local biomechanical factors. Thus, the pathophysiology of OA involves a combination of mechanical, biological, biochemical, molecular and enzymatic processes [1].

OA is characterized by the overproduction of cytokines and growth factors closely associated with functional alterations in the synovium, cartilage and subchondral bone [4]. The factors that trigger the pathophysiological process and symptoms of OA are unclear. Mechanical stress can activate the chondrocytes, causing them to release cytokines. After a phase of attempted cartilage repair characterized by increased proteoglycan synthesis, the phase of cartilage resorption starts. Breakdown of the cartilage extracellular matrix leads to the release of

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proinflammatory mediators, cytokines, nitric oxide, and enzymes produced by the chondrocytes (autocrine production) and synovial cells (paracrine production) [4–7]. In advanced OA, the chondrocytes differentiate into fibroblast-like cells or hypertrophic chondrocytes before undergoing premature death by necrosis and/or apoptosis [4–6,8].

Synovial inflammation occurs in OA, but the degree of inflammation varies across synovial sites and over time. The severity of synovitis ranges from clinically silent, in early-stage OA, to severe, with an appearance similar to the rheumatoid pannus [4,9]. During OA flares, synovitis contributes to the causes of pain, joint swelling and effusion. Synovitis can be visualized using MRI and leads to elevation of the serum ultrasensitive C-reactive protein level [10]. Importantly, the degree of macroscopic synovial membrane inflammation predicts radiological progression in knee OA [11]. Synovial membrane from joints with OA contains large numbers of macrophages and T cells [9,12]. Recent work has highlighted the major role of macrophages in the production of enzymes, including matrix metalloproteinase (MMP)-3, and in the production of proinflammatory cytokines, such as IL-1 and TNF-α, which, in turn, may activate the fibroblast synovial cells and chondrocytes [13].

Synovial inflammation is probably involved in the genesis of pain, as inflammatory mediators, such as prostaglandin E_2, bradykinin, 5-hydroxytryptamine and histamine, are released within the joint and increase the sensitivity of peripheral pain receptors [10]. Antidromic stimulation releases neuropeptides, such as substance P and calcitonin gene-related peptide, which contribute to synovial neoangiogenesis and local MMP production [10]. Moreover, TNF-α, IL-1β and IL-8 are involved in both central and peripheral pain transmission, as they induce persistent mechanical nociceptor hypersensitivity via the endogenous release of eicosanoids and sympathetic amines [14].

Synovial inflammation in OA results in the production of inflammatory mediators (VEGF, TGF-β, NF-κB, Cox 2, TNF-α and IL-1β). Among these mediators, IL-1β and TNF-α can stimulate their own production; activate chondrocytes and synovial cells to produce other cytokines such as IL-6, IL-8, leukocyte inhibitory factor and oncostatin M; and stimulate protease and prostaglandin E_2 production [4–7]. This creates a vicious circle between the altered cartilage and the synovial membrane [6].

Potential targets

Progress in our understanding of OA processes has led to the identification of promising therapeutic targets, with disease-modifying anti-OA drugs having the most potential. The effects of cytokines can be modulated at several levels, including production, maturation and activity. Many molecular pathways involved in OA pathogenesis have been explored as potential therapeutic targets, and many compounds have been tested in preclinical and clinical trials. IL-1β and TNF-α are emerging as treatment targets of choice. Inhibitors of these two proinflammatory cytokines are already available and are widely used in inflammatory joint diseases such as RA.

IL-1

Strong evidence supports a central role for IL-1β in cartilage breakdown in OA (Figure 1) [7]. IL-1β is detectable in the synovial fluid and cartilage extracellular matrix of joints with OA. IL-1β causes both cartilage matrix destruction by releasing enzymes (MMPs and aggrecanase) and blocks the normal production of cartilage matrix components (collagen type II and aggrecans). The production of IL-1β is both paracrine, by synoviocytes and macrophages in the inflamed synovium, and autocrine, by osteoarthritic chondrocytes [8]. In addition, IL-1β is biologically active, both because chondrocytes express functional receptors for IL-1β and because quantitative deficiencies exist in the systems that regulate IL-1β activity (the soluble form of type 2 receptor [IL-1RII] and the natural IL-1 inhibitor IL-1 receptor antagonist) [8].

Intra-articular IL-1β injection induces severe proteoglycan depletion in animals models of OA [15]. IL-1β inhibition *in vivo* in OA models partially prevents cartilage breakdown [16]. Nevertheless, low doses of IL-1β exert anabolic effects, leading to the unexpected result of IL-1 inhibition *in vivo* [17].

TNF-α

In OA, TNF-α also appears to play a pivotal role in inducing synovial membrane inflammation and mediating cartilage matrix degradation. Macrophages are major TNF-α producers and consequently regulate chondrogenesis [18]. TNF-α can induce chondrocyte apoptosis [6]. Chondrocytes express functional TNF-α receptors [4,7,19]. Soluble receptors can block the effects of TNF-α outside the cells.

In chondrocytes, TNF-α exerts not only catabolic effects, but also major antianabolic effects [7]. The effect of TNF-α on chondrocytes

is similar to that of IL-1β overall, albeit less marked. TNF-α potentiates the effects of IL-1β. Both cytokines act within a complex network by inducing the production of other cytokines such as IL-6, -8, -11 and -17, and leukemia inhibitory factor [7,20]. Moreover, IL-1 acts in synergy with other cytokines, including TNF-α, IL-6/-6R and oncostatin M, to stimulate collagen and aggrecan breakdown [7,10,21].

In all likelihood, TNF-α is involved in OA progression. TNF-α is found in synovial fluid from OA joints, in higher concentrations than those of IL-1β [7]. Immunohistochemistry studies have established that TNF-α and its active receptor are expressed *in situ* by osteoarthritic chondrocytes [6,7].

Other mediators

In OA, particularly in the early stages, cartilage repair processes occur. This anabolic response is caused by chondrocyte activation by growth factors that stimulate the production of matrix proteins. The most powerful growth factors involved in cartilage repair include IGF-1, basic FGF, PDGF, bone morphogenetic proteins and TGF-β [5,19]. There is increasing evidence that TGF-β plays a prominent role in OA via multiple and apparently contradictory effects [19]. TGF-β inhibition results in increased proteoglycan loss and cartilage damage, and exogenous TGF-β administration limits the cartilage damage. In addition, TGF-β counteracts the effects of IL-1 [19]. However, intra-articular injection of TGF-β1 in high doses leads to proteoglycan depletion, synovial proliferation and osteophyte production [6,19].

Finally, TNF-α is probably biologically active in the joint, playing a major role in OA progression. IL-1β and TNF-α seem to act independently of each other in OA, contrary to what happens in RA [22]. IL-1β blockade *in vitro* does not block the action of TNF-α and *vice versa* [22]. The balance among the IL-1β, TNF-α and TGF-β signaling pathways is crucial for the maintenance of articular cartilage homeostasis, and disruption of this balance probably makes a major contribution to the pathogenesis of OA [23].

Taken in concert, these data suggest that blocking IL-1β and/or TNF-α may hold promise for the treatment of OA, both to slow disease progression and to alleviate the pain. As growth factors exert multiple effects at various sites in the joint, TGF-β may be of special interest. TGF-β inhibition or administration should be compartmentalized [19].

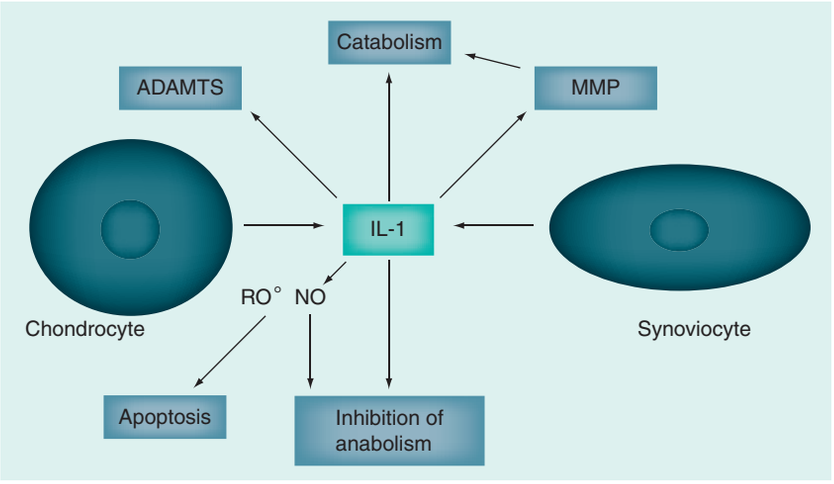

Figure 1. Effect of IL-1: a pivotal role in cartilage metabolism in osteoarthritis joint.
ADAMTS: A disintegrin and metalloproteinase with thrombospondin; MMP: Matrix metalloproteinase; NO: Nitric oxide; RO: Free radical.
Adapted with permission from [41].

Furthermore, other biochemical pathways are being studied (Box 1). The results will probably suggest new targets for disease-modifying anti-OA drugs.

Which route of administration?

Osteoarthritis can affect a single joint (usually the knee or hip) or multiple joints (polyarticular or hand OA). However, given the absence of a known systemic disease mechanism, local administration seems preferable for biologic

Box 1. Tissue-specific therapeutic targets for the development of disease-modifying antiosteoarthritis drugs.

Cartilage
- Inhibiting catabolism
  - Protease inhibitors of MMPs and ADAMTSs
  - Inducible nitric oxide synthase inhibitor
  - Cell-signaling pathway inhibitors: MAPK, JNK, p38 and ERK1/2, for example
  - Combined inhibitor of eicosanoids (5-LOX and COX)
- Stimulating anabolism
  - Growth factors: TGF-β1, IGF-1, basic FGF, BMP-2, BMP-4 and BMP-7
  - Sonic hedgehog

Synovial membrane
- Cytokines and IL-1β inhibitors (e.g., interleukin-converting enzyme inhibitor, neutralizing antibodies, soluble receptors, receptor inhibitors and PPAR-γ agonists)
- ROS inhibitors

Subchondral bone
- Inhibitors of bone resorption: bisphosphonates, strontium ranelate, calcitonin, protease inhibitors (MMP-13, cathepsin K), osteoprotegerin, RANKL inhibitors and neutralizing antibodies
- Stimulation of bone formation, PTH, SERM and estrogens

ADAMTS: A disintegrin and metalloproteinase with thrombospondin; BMP: Bone morphogenetic protein; MMP: Matrix metalloproteinase; PTH: Parathyroid hormone; ROS: Reactive oxygen species; SERM: Selective estrogen receptor modulator.
Data taken from [4,38,39].

therapy in OA, most notably at the knee. The aim is to obtain high concentrations within the joint with minimal systemic exposure. In contrast to the synovial membrane and subchondral bone, the joint cartilage contains no vessels or nerves and is therefore difficult to reach using systemic routes of administration. In addition, intra-articular injection is an effective means of administering drugs with low oral bioavailability. Disadvantages of the intra-articular route include the need for strict injection within the joint cavity, difficulties in accessing small joints, risks associated with repeated injections and short residency time of the injected drugs, caused by efficient lymphatic drainage [24]. In contrast to knee OA, hand OA is a polyarticular disease and may, therefore, be related, in part, to systemic factors. In addition, hand OA affects small joints such as the interphalangeal joints. In this case, systemic administration of biologics may be more appropriate than intra-articular injections.

Determining the optimal route of administration of the biologics in OA remains a challenge. Drug carrier systems such as liposomes, micro- or nano-particles, and hydrogels hold promise, and are being actively developed [24].

Which biotherapy for which patient?

Currently, it is too early to recommend biologics in OA. The number of clinical studies evaluating the efficacy of biologics in OA is still too small. However, interventions on a number of targets have been found to provide pain relief and to slow disease progression in animal models of OA.

Blocking IL-1

The effects of IL-1 can be inhibited *in vitro* and *in vivo* by a natural competitive inhibitor, IL-1 receptor antagonist (IL-1Ra); and by soluble receptors (Figure 2). IL-1Ra belongs to the IL-1 family and binds to the IL-1 receptors but does not induce an intracellular response. IL-1Ra blocks the effects of IL-1 by preventing the interaction of IL-1 with the cell surface receptors.

Based on encouraging results in animals [15], we conducted the first clinical trial to evaluate the safety of intra-articular IL-1Ra in patients who had symptomatic knee OA without synovial fluid effusion [25]. We found that IL-1Ra was well tolerated up to a dose of 150 mg. In the 13 patients who received 150 mg of IL-1Ra, significant improvements in pain and the Western Ontario and McMaster Universities OA Index (WOMAC) total score were noted until month 3 (Figure 3) [25].

Although promising, the results of these studies did not constitute evidence that IL-1Ra is more effective than a placebo. We therefore performed a multicenter, double-blind, placebo-controlled study [26]. Patients with symptomatic knee OA were randomized in three groups treated with a single intra-articular injection of 150 mg IL-1Ra, 50 mg IL-1Ra and a placebo, respectively. In the 160 patients who completed the study, IL-1Ra was not better than the placebo after 4 weeks in terms of knee pain, function, stiffness or measures of cartilage turnover (Figure 4) [26]. A trend towards decreased pain with IL-1Ra 150 mg versus placebo was noted on day 4. In this trial, IL-1Ra was well tolerated [26]. Moreover, encouraging results were obtained in an ancillary study conducted in seven patients with knee OA, of whom six received a single intra-articular injection of 150 mg and reported decreases in pain intensity that correlated with improvements in MRI synovial scores [27]. However, similar to our trial, a double-blind randomized trial of monoclonal human anti-IL-1R1 antibody given by intravenous infusion for 3 months versus placebo in 149 patients with symptomatic knee OA, with the WOMAC pain score at 6 weeks as the primary efficacy end point, found that the only significant difference between the placebo and treatment groups was a decrease in ultrasensitive C-reactive protein with treatment [28]. Overall, although data in humans are disappointing for the moment, there is a sound rationale for using IL-1β blockade to treat OA, and highly promising results have been obtained using this strategy in animal models. Conceivably, the rapid clearance and short plasma half-life of IL-1Ra (approximately 4 h) may preclude a meaningful effect on IL-1β [26]. Moreover, intra-articular IL-1Ra injection may have limited effects in patients with knee OA, who have a high ratio of endogenous IL-1Ra over IL-1β in the synovial fluid [29]. However, in knee OA, a high ratio of endogenous IL-1Ra/IL-1β correlated neither with pain nor with the Lequesne index [29].

Strategies that may deserve evaluation include the use of higher doses of IL-1Ra and the administration of repeated intra-articular doses. However, these two strategies would be expected to increase the risk of adverse events. Few data are available on the use of IL-1Ra in hand OA. In a recent limited study in three patients with erosive hand OA, daily subcutaneous injections of 100 mg of IL-1Ra significantly improved the pain and global disability, and significantly increased the rate of nonsteroidal anti-inflammatory drugs discontinuation, with these effects persisting for up to 3 months [30].

Blocking TNF-α

Given the major role played by TNF-α in the pathophysiology of OA, TNF-α antagonist therapy would be expected to have therapeutic effects. In theory, these potential effects should be more marked in patients with synovitis and joint effusion, as TNF-α levels in OA synovial fluid are higher than IL-1β levels [7].

Most studies evaluating TNF-α antagonists in OA were done in patients with hand OA. Erosive hand OA is a distinctive form of finger OA that affects several interphalangeal joints, and exhibits systemic and inflammatory features reminiscent of RA or psoriatic arthritis [31]. Ultrasensitive C-reactive protein levels are higher in erosive hand OA than in nonerosive hand OA, indicating the presence of systemic inflammation. Currently available treatments for erosive hand OA have limited efficacy [31].

In 2004, we reported the case of a patient with erosive hand OA in whom a single infliximab infusion produced therapeutic effects that lasted several months [32]. The first pilot study conducted in erosive hand OA evaluated both the efficacy and the safety of adalimumab [33]. The 12 included patients had active disease (visual analog scale pain score >40 mm and mean values of nine tender and eight swollen joints) and received six subcutaneous injections of 40 mg adalimumab, once every 2 weeks over 12 weeks. Adalimumab treatment did not significantly improve the signs or symptoms, and 11 patients failed to achieve an Americam College of Rheumatology 20% improvement (ACR20) response. However, trends suggested some improvement in all efficacy end points and some of the patients benefited from the treatment [33].

More recently, the structural effects of 1 year of adalimumab therapy were evaluated in a placebo-controlled trial that included 60 patients with erosive hand OA. Adalimumab had a disease-modifying effect in the subgroup of patients who had palpable synovial effusions of the interphalangeal joints at baseline [34]. The structural effects of infliximab, another TNF-α antagonist, were evaluated in patients who had both RA and hand OA, and who were participating in a study of therapeutic strategies for early-stage RA [35]. At baseline, the incidence of hand OA was not significantly different between the infliximab users and non-users. After 3 years of follow-up, hand OA progression was noted in 38% of infliximab non-users compared with only 10% of infliximab users. This study suggests a disease-modifying effect of TNF-α antagonist therapy in patients having both RA and hand OA [35].

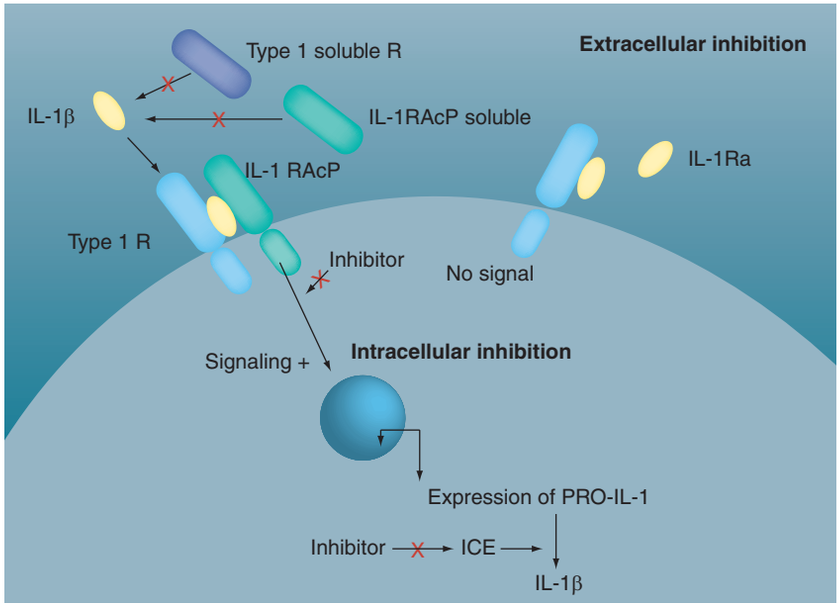

Figure 2. Extracellular and intracellular sites of IL-1β blockade.
ICE: Interleukin converting enzyme; IL-1Ra: IL-1 receptor antagonist; IL-1RAcP: IL-1 receptor accessory protein; PRO-IL-1: Proform of IL-1; R: Receptor.
Reproduced with permission from [41].

A single study has evaluated intra-articular TNF-α antagonist injections in hand OA [36]. The ten women included in this single-blind trial received a monthly injection of 0.2 ml of infliximab in the affected interphalangeal joints of the hand where the disease was most severe. Saline solution was injected intra-articularly in the other hand, which served as the control.

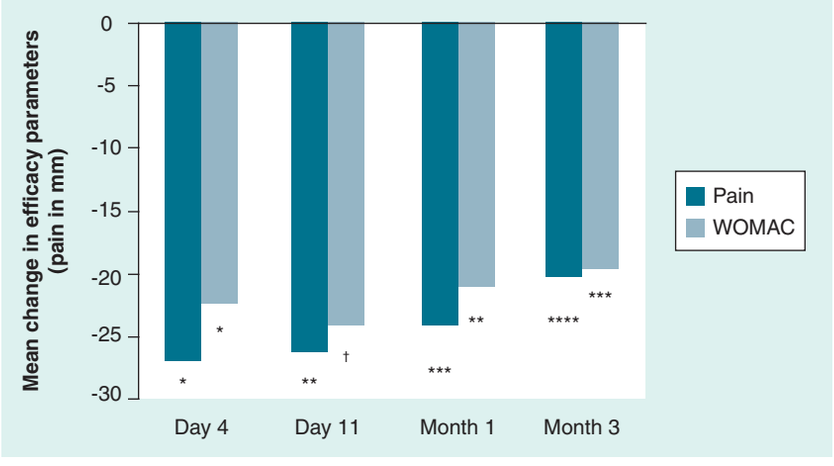

Figure 3. Effect on the Western Ontario and McMaster Universities Osteoarthritis Index score (pain intensity) of a single intra-articular injection of IL-1 receptor antagonist (anakinra 150 mg) in 13 patients with symptomatic knee osteoarthritis. Shows the absolute change from baseline in efficacy parameters.
*p = 0.001; **p = 0.002; ***p = 0.005; ****p = 0.006 compared with baseline.
†p < 0.001 compared with baseline.
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
Reproduced with permission from [25].

After 6 months, improvements were noted in spontaneous pain and pain induced by lateral pressure. This improvement became significant after 1 year, whereas no significant change was found in the placebo group. After 1 year, there was a nonsignificant decrease in structural damage in the infliximab-treated hands and a trend toward disease progression in the control hands. Although this limited study was hampered by numerous methodological flaws, the results may suggest a symptomatic effect and a possible disease-modifying effect of intra-articular infliximab in erosive hand OA [36].

To our knowledge, there is a single report of TNF-α antagonist therapy in knee OA. A retired rheumatology professor with incapacitating knee OA self-injected adalimumab into the joint every 2 weeks at first then every 3–6 weeks [37]. Rapid improvements occurred in the clinical symptoms, most notably pain and walking difficulties, and persisted for 6 months. More importantly, the subchondral edema seen on the initial MRI was almost completely resolved on the repeat MRI perfromed 6 months later [37].

The use of TNF-α antagonist therapy in OA faces two major challenges: the half-life of TNF-α antagonists is fairly short and these drugs are known to increase the risk of infection. Nevertheless, the inflammation that characterizes hand OA warrants consideration of proinflammatory cytokine blockade as a possible future treatment option. One means of circumventing the problems raised by the short half-life of TNF-α antagonists (and IL-1Ra) may be to use a gene-therapy approach.

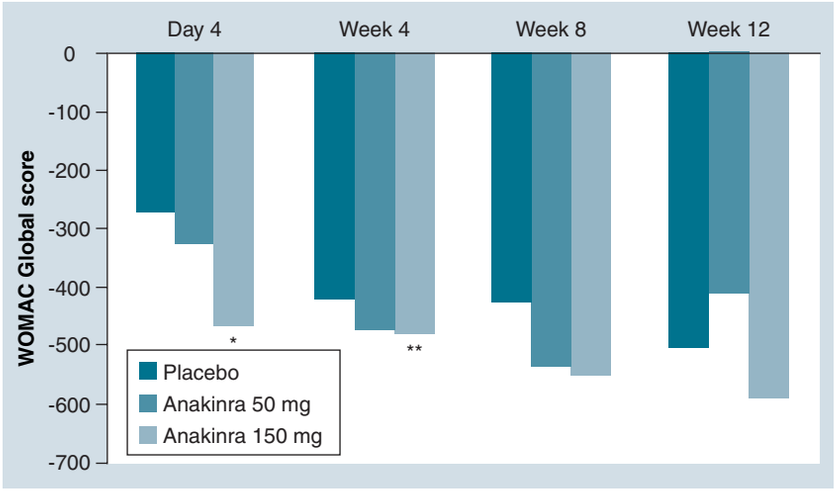

Figure 4. Effect on the Western Ontario and McMaster Universities Osteoarthritis Index global score 4 weeks after a single intra-articular injection of IL-1 receptor activator (anakinra 50 and 150 mg) versus placebo in 160 intention-to-treat patients with symptomatic knee osteoarthritis.
*p = 0.05; ** p < 0.77.
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
Reproduced with permission from [27].

Gene therapy

Gene therapy can be used in OA as a drug delivery system to modify or restore the balance between anabolic and catabolic factors, or to modulate the proinflammatory mediators. Gene therapy holds considerable potential for improving OA, as high concentrations of biologics can be achieved in the joint and sustained over time. Various *ex vivo* or *in vivo* strategies using nonviral and viral vectors can be considered. Viral vectors have the advantage of ensuring highly efficient transfer to a large percentage of cells, while maintaining high levels of protein expression over long periods [4]. Since OA can affect a single knee, local gene therapy holds promise as an affordable and effective treatment strategy [38]. In both the cartilage and the synovium, catabolic factors and cytokines should be either decreased or eliminated. By contrast, growth factors, IL-1Ra, soluble IL-1RII and soluble TNF receptor should be stimulated **(Box 2)** [4].

At present, gene therapy in OA is chiefly experimental. Most gene therapy studies in OA models were conducted using the *IL-1Ra* gene [38]. The first trial of *IL-1Ra* gene transfer in OA joints was performed in a model of canine knee OA induced by anterior cruciate ligament injury [39]. *IL-1Ra* gene transfer was achieved via intra-articular injections of transduced synovial cells. Despite low levels of expression of the therapeutic moleule in the synovial fluid, IL-1Ra production was sufficient to decrease the progression of the cartilage lesions [39].

This work was followed by several other preclinical studies. In addition to IL-1Ra, chondrogenesis-stimulating differentiation factors such as IGF-1, FGF-2, bone morphogenetic protein-2, -4 and -7, and TGF-β1 have shown promise for inducing cartilage repair when administered by gene transfer in animal models [38]. Several preclinical or clinical trials of *ex vivo* gene *TGF-β1* transfer to osteoarthritic joints are underway [38]. However, a major concern with viral vectors is the risk of insertional mutagenesis or induction of a systemic inflammatory response [38]. To date, the safest viral vector seems to be the adeno-associated virus. Another concern is that growth factor gene transfer may result in systemic exposure with a risk of adverse effects at a distance from the joints and of local stem cell dedifferentiation to an osteogenic lineage [24].

Future perspective

At present, biologics are used chiefly on the basis of studies in patients with chronic inflammatory joint disease, most notably RA. The risk:benefit ratio of biologics will be a major limiting factor in OA [40]. Although OA patients usually have normal immune functions, the precautions recommended for inflammatory joint disease will have to be followed. In theory, the risk of malignancy associated with biologics (if any) is considerably lower in OA patients than in patients with inflammatory joint disease.

The intra-articular route will probably be preferred, both to diminish the risk of potential adverse events and to target not only the synovial membrane, but also probably the superficial cartilage layers. Intra-articular administration makes sense for the treatment of large joints such as the knee or hip. For hand OA, the situation is different; the interphalangeal joints are small, multiple joints are involved, and, in the erosive form of the disease, the pain is severe and the disability substantial. Thus, in patients with hand OA, the systemic route may be more appropriate for IL-1Ra and TNF-α antagonists. Gene therapy (most notably to transfer *IL-1Ra* and *TGF-β1* genes) may be used as a local treatment or as a facilitated local treatment.

In everyday practice, the crucial problem will be to select patients for biologic therapy, and then to determine the modalities and frequency of administration. The dosage, timing and duration of treatments need to be better evaluated in clinical trials, and to be specified drug by drug. One of the major problems will be finding a good compromise between efficacy in terms of preventing the structural progression of the disease and the risk of adverse events linked to the use of biotherapy. Both the available clinical trials and the lessons from everyday practice indicate that biological therapy should be reserved for periods of inflammatory disease activity [40]. During these periods, chondrolysis may occur as a result of active synovitis [11]. However, overt synovitis means that the disease is in a stage where cartilage destruction is occurring. Thus, targeted administration based on the patient's complaints is probably preferable to continuous administration in order to, hopefully, slow the disease rather than prevent it. There is a need for identifying criteria that predict rapidly destructive OA, as patients meeting these criteria would probably be good candidates for biologic therapy.

Box 2. Gene therapy for osteoarthritis.

Potential targets

- Cartilage
  - Anabolic factors: TGF-β1, IGF-1, basic FGF, BMP-2, BMP-4, BMP-7 and sonic hedgehog
  - Catabolic factors: MMPs and nitric oxide
  - Apoptotic factors: caspases and ceramides
- Synovial membrane
  - Proinflammatory cytokines: IL-1β and TNF-α
  - Anti-inflammatory cytokines: IL-4, -10 and -13
- Cytokine receptors: IL-1Ra, soluble IL-1RII and soluble TNF receptor
- Subchondral bone?

Strategies

- Gene replacement
- Gene addition
- Gene control

BMP: Bone morphogenetic protein; IL-1Ra: IL-1 receptor antagonist; IL-1RII: IL-1 type 2 receptor; MMP: Matrix metalloproteinase.
Adapted from [4,38].

In conclusion, biologics will probably be introduced into the treatment armamentarium for OA in the future. The first results may be obtained for hand OA (there is currently one ongoing trial with adalimumab). We hypothesize that TNF-α antagonist therapy is appropriate in OA with joint effusion and synovitis. IL-1 inhibitors may be best viewed as long-term chondroprotective drugs. On the other hand, when the synovium is not involved (outside of disease flares), transfer of the *TGF-β* gene (and/or genes for other growth factors) may be a good alternative. Further studies are required to confirm these hypotheses. We agree with Blom *et al.* [19] that, to restore cartilage homeostasis and to stimulate proper repair, biologic therapy targeting both anabolic and catabolic mediators will produce the best results. We hope that biologics will fulfil the hope placed on them based on their clinical efficacy with effective chondroprotection and a limited number of adverse events.

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Disclosure

A French version has been published in the Presse médicale *by X Chevalier.*

Executive summary

Osteoarthritis

- Osteoarthritis (OA) is the most prevalent articular disease; however, we lack an efficient therapy to slow down the progression of the disease.

Pathophysiology

- Osteoarthritis is a disease marked by an imbalance between anabolism and catabolism. The synovial membrane inflammation is marked by the production of several proinflammatory mediators such as cytokines and enzymes. Blocking those cytokines appears to be a promising tool.

Potential targets

- Among the cytokines that are involved in the disease process, IL-1 is certainly the main cytokine, which, in part, governs the chondrolysis in OA. TNF-α also presents the same catabolic properties towards the cartilage matrix and is also regarded as cytokine involved in synovial membrane inflammation. Both cytokines are produced in the cartilage and the synovium during the OA process. In animal models of OA, blocking IL-1 production demonstrated encouraging results.

Which route of administration?

- For large joints such as the knee, local administration of anticytokine drugs appears logical and may also decrease the risk of systemic side effects. By contrast, for polyarticular digital OA, a systemic route of administration should be considered.

Which biotherapy for which patient?

- Blocking IL-1
  - Only one randomized placebo-controlled trial using local injection of IL-1 receptor antagonist has been performed (single intra-articular injection of 50 and 150 mg). The overall result was negative on evolution of pain at 1 month.
- Blocking TNF-α
  - Inhibitors of TNF have been tried in patients with digital hand OA using a systemic route of administration (repeated subcutaneous injections). Results are encouraging and show some benefit on pain and disease progression.

Gene therapy

- The main advantage of this modality is the possibility of prolonging the local production of cytokine inhibitor. However, this therapy needs to be better evaluated in humans, notably in terms of safety.

Future perspective

- Inhibition of cytokine production in OA is a major challenge. Several points still need to be addressed: which therapy to which patient? When during the course of the disease? What are the best therapeutic modalities in terms of dosage, time and duration of biotherapy in OA?

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Felson DT, Lawrence RC, Dieppe PA *et al.*: Osteoarthritis: new insight. Part 1: the disease and its risk factors. *Ann. Intern. Med.* 133, 635–646 (2000).

2 Zhang W, Moskowitz RW, Nuki G *et al.*: OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr. Cartil.* 16, 137–162 (2008).

3 Zhang W, Doherty M, Leeb BF *et al.*: EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* 66, 377–388 (2007).

4 Pelletier JP, Martel-Pelletier J, Abramson SE: Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum.* 44, 1237–1247 (2001).

▪ **Comprehensive review of inflammation in osteoarthritis.**

5 Chevalier X: *Physiopathologie de l'Arthrose.* Elsevier Masson SAS, Paris, France (2008).

6 Chevalier X: Physiopathogenesis of osteoarthritis. The osteoarthritic cartilage. *Presse Med.* 27, 81–87 (1998).

7 Goldring SR, Goldring MB: The role of cytokines in cartilage matrix degeneration in osteoarthritis. *Clin. Orthop. Rel. Res.* 427, S27–S36 (2004).

8 Chevalier X: Upregulation of enzymatic activity by interleukin-1 in osteoarthritis. *Biomed. Pharmacother.* 51, 58–62 (1997).

9 Benito MJ, Veale DJ, Fitzgerald O, Van den Berg WB, Bresnihan B: Synovial tissue inflammation in early and late osteoarthritis. *Ann. Rheum. Dis.* 64, 13–17 (2005).

▪▪ **Important work demonstrating the presence of synovitis in the early phase of the osteoartritic process.**

10 Bonnet CS, Walsh DA: Osteoarthritis, angiogenesis and inflammation. *Rheumatology (Oxford)* 44, 7–16 (2005).

11 Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M: Synovitis predicts the arthroscopic progression of medial tibiofemoral knee osteoarthritis. *Arthritis Rheum.* 44(Suppl. 9), 952 (2001).

▪▪ **Demonstrates the link between osteoarthritis progession and the degree of synovial membrane inflammation at baseline.**

12 Pessler F, Dai L, Diaz-Torne C *et al.*: The synovitis of "non-inflammatory" orthopaedic arthropathies: a quantitative histological and immunohistochemical analysis. *Ann. Rheum. Dis.* 67, 1184–1187 (2008).

13 Blom AB, Lent PL, Libregts S *et al.*: Crucial role of macrophages in matrix metalloproteinases-mediated cartilage destruction during experimental osteoarthritis. *Arthritis Rheum.* 56, 147–157 (2007).

▪ **Focuses on the role of synovial macrophages in cartilage matrix destruction.**

14 Sachs D, Cunha FQ, Poole S *et al.*: Tumour necrosis factor-α, interleukin-1β and interleukin-8 induce persistent mechanical nociceptor hypersensitivity. *Pain* 96, 89–97 (2002).

15 Chandrasekhar S, Harvey AK, Hrubey PS: Intra-articular administration of interleukin-1 causes prolonged suppression of cartilage proteoglycan synthesis in rats. *Matrix* 12, 1–10 (1992).

16 Caron JP, Fernandes JC, Martel-Pelletier J *et al.*: Chondroprotective effect of intra-articular injections of interleukin-1 receptor antagonist in experimental osteoarthritis. Suppression of collagenase-1 expression. *Arthritis Rheum.* 39, 1535–1544 (1996).

▪ **Pioneering work on cytokine targeting in an experimental model of osteoarthritis.**

17 Clements KM, Price JS, Chambers MG, Visco DM, Poole AR, Mason RM: Gene deletion of either interleukin-1β, interleukin-1β converting enzyme, inducible nitric oxide synthase, or stromelysin 1 accelerates the development of knee osteoarthritis in mice after surgical transection of the medial collateral ligament and partial medial menisectomy. *Arthritis Rheum.* 48, 3352–3363 (2003).

18 Bloom AB, van Lent PL, Holthuysen AE *et al.*: Synovial lining macrophages mediate osteophyte formation during experimental osteoarthritis. *Osteoarthr. Cartil.* 12, 627–635 (2004).

19 Blom AB, van der Kraan PM, van der Berg WB: Cytokine targeting in osteoarthritis. *Curr. Drug Targets* 8, 283–292 (2007).

▪ **A comprehensive overview of cytokine targeting in osteoarthritis.**

20 Henrotin Y, Sanchez C, Balligand M: Pharmaceutical and neutraceutical management of canine osteoarthritis: present and future perspectives. *Vet. J.* 170, 113–123 (2005).

21 Milner JM, Elliott SF, Cawston TE: Activation of procollagenases is a key control point in cartilage collagen degradation: interaction of serine and metalloproteinase pathways. *Arthritis Rheum.* 44, 2084–2096 (2001).

22 Bondeson J: Activated synovial macrophages as target for osteoarthritis. *Curr. Drug Targets* 11, 576–585 (2010).

23 Roman-Blas JA, Stokes DG, Jimenez SA.: Modulation of TGF-β signaling by proinflammatory cytokines in articular chondrocytes. *Osteoarthr. Cartil.* 15, 1367–1377 (2007).

24 Chevalier X: Intra-articular treatments for osteoarthritis: new perspectives. *Curr. Drug Targets* 11, 546–560 (2010).

▪ **Comprehensive overview in the field of intra-articular treatment in osteoarthritis.**

25 Chevalier X, Giraudeau B, Conrozier T *et al.*: Safety study of intra-articular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. *J. Rheumatol.* 32, 1317–1323 (2005).

26 Loeuille D, Chary-Valckeneare I, Goebel G *et al.*: MRI evaluation of the synovial membrane after single intra-articular injection of anakinra in 7 patients with osteoarthritis of the knee suggests anti-inflammatory effect. *Arthritis Rheum.* 52(Suppl. 9), S70–S94 (2005).

27 Chevalier X, Goupille P, Beaulieu AD *et al.*: Intra-articular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 61, 344–352 (2009).

▪▪ **Pioneering work on cytokine targeting by a single intra-articular injection of IL-1 receptor activator in patients with knee osteoarthritis. Results show no difference in terms of pain evolution between verum and placebo at 1 month.**

28 Cohen S, Proudman S, Kivitz A *et al.*: Results of a randomised controlled trial of AMG 108 (a fully monoclonal human antibody to IL1R type 1) in patients with osteoarthritis of the knee. *Arthritis Rheum.* 56(Suppl. 9), 1684 (2007).

29 Richette P, François M, Vicaut E *et al.*: A high interleukin 1 receptor antagonist/IL-1β ratio occurs naturally in knee osteoarthritis. *J. Rheumatol.* 35, 1650–1654 (2008).

30 Bacconnier L, Jorgensen C, Fabre S: Erosive osteoarthritis of the hand: clinical experience with anakinra. *Ann. Rheum. Dis.* 68, 1078–1079 (2009).

31 Punzi L, Ramonda R, Sfriso P: Erosive osteoarthritis. *Best. Pract. Res. Clin. Rheumatol.* 18, 739–758 (2004).

32 Avouac J, Marini-Portugal A, Chevalier X: A propos d'un cas d'arthrose digitale érosive: réponse spectaculaire aux anti-TNFα. *Rev. Rhum.* 71, 158 (2004).

33 Magnano MD, Chakravarty EF, Broudy C *et al.*: A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. *J. Rheumatol.* 34, 1323–1327 (2007).

34 Verbruggen G, Wittoek R, Vander C *et al.*: Preliminary results of a Phase II placebo controlled trail with adalimumab in erosive hand osteoarthritis: predictors of erosions and the potential effect of adalimumab in specific sub groups. *Arthritis Rheum.* 60(Suppl. 10), 856 (2009).

▪ **A 1-year randomized placebo controlled trial using repeated subcutaneous injections of inhibitors of TNF-α in patients with digital osteoarthritis. Main criteria focused on the structural progression and showed encouraging results in joints with clinical signs of inflammation.**

35 Güler-Yüksel M, Kloppenburg M, Allaart CF *et al.*: Infliximab might be protective against progressive interphalangeal osteoarthritis. *Ann. Rheum. Dis.* 67(Suppl. II), 630 AB0714 (2008).

36 Fioravanti A, Fabbroni M, Cerase A, Galeazzi M: Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. *Rheumatol. Int.* 29, 961–965 (2009).

37 Grunke M, Schulze-Koops H: Successful treatment of inflammatory knee osteoarthritis with tumour necrosis factor blockade. *Ann. Rheum. Dis.* 65(4), 555–556 (2006).

38 Evans CH, Ghivizzani SC, Robbins PD: Gene therapy of the rheumatic diseases: 1998 to 2008. *Arthritis Res. Ther.* 11, 209 (2009).

▪ **Comprehensive review on gene therapy.**

39 Pelletier JP, Caron JP, Evans C *et al.*: *In vivo* suppression of early experimental osteoarthritis by interleukin-1 receptor antagonist using gene therapy. *Arthritis Rheum.* 40, 1012–1019 (1997).

40 Pelletier JP, Martel-Pelletier J: DMOAD developments: present and future. *Bull. NYU Hosp. Jt Dis.* 65, 242–248 (2007).

41 Chevalier X, Richette P, Compaore C: Biothérapies en développement dans l'arthrose. In: *Biothérapies en Rhumatologie.* Boissier MC (Ed.). Springer, Paris, France, 147–159 (2010).