Chondroprotective drugs in degenerative joint diseases

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Catabolic cytokine and anabolic growth factor pathways control destruction and repair in osteoarthritis (OA). A unidirectional TNF-α/IL-1-driven cytokine cascade disturbs the homeostasis of the extracellular matrix of articular cartilage in OA. Although chondrocytes in OA cartilage overexpress anabolic insulin-like growth factor (IGF) and its specific receptor (IGFRI) autocrine TNF-α released by apoptotic articular cartilage cells sets off an auto/paracrine IL-1-driven cascade that overrules the growth factor activities that sustain repair in degenerative joint disease. Chondroprotection with reappearance of a joint space that had disappeared has been documented unmistakably in peripheral joints of patients suffering from spondyloarthropathy when treated with TNF-α-blocking agents that repressed the unidirectional TNF-α/IL-1-driven cytokine cascade. A series of connective tissue structure-modifying agents (CTSMAs) that directly affect IL-1 synthesis and release in vitro and down-regulate downstream IL-1 features, e.g. collagenase, proteoglycanase and matrix metalloproteinase activities, the expression of inducible nitric oxide synthase, the increased release of nitric oxide, and the secretion of prostanoids E2, IL-6 and IL-8, have been shown to possess disease-modifying OA drug (DMOAD) activities in experimental models of OA and in human subjects with finger joint and knee OA. Examples are corticosteroids, some sulphated polysaccharides, chemically modified tetracyclines, diacetylrhein/rhein, glucosamine and avocado/soybean unsaponifiables.

Key words: Osteoarthritis, TNF-α, IL-1, Chondroprotection, DMOADs.

Loss of function is the consequence of anatomical changes in the tissues of joints with osteoarthritis (OA). Interfering with the anatomical progression of OA appears to be a method to preserve normal joint function. Substances that protect articular cartilage during the course of OA have been termed chondroprotective agents. When they appear to alter the course of the disease these agents may be termed disease-modifying OA drugs (DMOADs) [1]. Pain in OA joints has been attributed to different causes that are secondary to the anatomical changes, e.g. inflammatory events in the synovium and subchondral intraosseous hypertension due to venous congestion. This review will deal with the DMOAD aspects of chondroprotective therapy and not with the alleviation of the clinical symptoms that can eventually occur when patients are administered DMOAD therapy.

Homeostasis of the extracellular matrix of healthy articular cartilage

Homeostasis of the extracellular matrix (ECM) of articular cartilage is dependent on the responses of articular cartilage cells to auto- and paracrine anabolic and catabolic pathways. The most relevant growth factors and cytokines known to be involved in cartilage metabolism are produced by chondrocytes themselves [2, 3]. Synthesis and accumulation of the ECM is regulated by locally produced growth factors, such as the insulin-like growth factors (IGFs) and transforming growth factor-β (TGF-β). A specific regulatory role for TGF-β has been suggested under pathological conditions [4], and a large body of experimental data has substantiated the importance of IGF-1 as a promoter of growth and matrix synthesis by chondrocytes in healthy articular cartilage. IGF-1 enhances aggrecan synthesis by articular cartilage cells or explants [5–10] and in vivo in animal models [11]. Turnover and degradation of the matrix are dependent on the responsiveness of the articular cartilage cell to catabolic cytokines, of which IL-1α and β are the main agonists [12, 13]. Besides its ability to induce degradation of articular cartilage, IL-1 has been shown to suppress the synthesis of aggrecan and collagen by the chondrocyte [14, 15]. This reduction in the production of ECM compounds is mediated in part by IL-1-induced generation of nitric oxide (NO) [16]. The IL-1 effects are mediated through a high-affinity cell surface receptor (IL-1RI) [17, 18]. Important controlling factors of IL-1 activity are IL-1 receptor family-related proteins, amongst which the type 2 IL-1 decoy receptor (IL-1RII) is expressed on the chondrocyte plasma membrane and binds IL-1α and β, but does not transmit the IL-1 signals [19, 20]. Interestingly, IGF was shown to up-regulate the IL-1 decoy receptor IL-1RII, thereby reversing IL-1-activity [21]. This finding concurred with the observation that IGF-1 directly decreases both the basal and the cytokine-stimulated degradation [22] and depression of the ground substance of articular cartilage [21]. By up-regulation of IL-1RII, IGF-1 thus protects cartilage ECM against IL-1-induced destruction (Fig. 1A).
OA cartilage compared with morphologically normal cartilage increases in metalloproteinase activities, which were higher in catabolic cytokine levels are embodied by well-documented restoration of the ECM. activity in cartilage cells that overexpress IGF-1 leads to IGF-1/IGF-RI growth factor activity. (C) Repression of IL-1 reasons, chondrocytes in OA cartilage overexpress anabolic cascade, resulting in resorption of the ECM. For unknown reasons, chondrocytes in OA cartilage overexpress anabolic IGF-1/IGF-R1 growth factor activity. (C) Repression of IL-1 activity in cartilage cells that overexpress IGF-1 leads to restoration of the ECM.

The pathology of OA-druggable cytokine and growth factor pathways
The up-regulation of both catabolic [2, 3, 23, 24] and anabolic [2, 3, 23–26] pathways has been reported in OA chondrocytes and cartilage. A correlation with the occurrence and degree of OA pathology was noted for IL-1β [2, 3, 27] and these elevated catabolic cytokine levels are embodied by well-documented increases in metalloproteinase activities, which were higher in OA cartilage compared with morphologically normal cartilage from the same joint [27–30]. In addition, an increase in IL-1RI receptor density was found in OA chondrocytes compared with normal chondrocytes. mRNA and protein levels of IGF-1 and its receptor IGFRI were significantly higher in fibrillated OA cartilage than in non-fibrillated cartilage of OA hip and knee joints [23, 26]. The strongest IGF-1 message signals or protein levels were observed in chondrocytes of more advanced lesions [23, 26]. When cells obtained from normal and OA tissues from the same human knee joints were compared, cell-associated aggrecan and type II collagen were significantly reduced around the chondrocytes obtained from pathological tissue. Concomitantly, chondrocytes from fibrillated OA cartilage expressed significantly higher intracellular IL-1α and β levels and up-regulated plasma membrane-bound IL-1RI. At the same time, significantly higher intracellular IGF-1 levels and plasma membrane-bound IGF-R1 were observed. Surprisingly, in the presence of this enhanced IGF activity, the expression of the plasma membrane-bound IL-1RII decoy receptor was decreased in OA chondrocytes [26]. The decreased levels of plasma membrane IL-1RII decoy receptor on the OA chondrocytes may be attributed to interferences from other autocrine cytokine pathways. In this context, TNF-α has been shown to cause rapid shedding of IL-1RII from myelomonocytic cell membranes [31, 32]. A similar effect of TNF-α on articular cartilage cells still needs to be demonstrated. The presence of TNF-α in mechanically abused cartilage, however, has been exemplified repeatedly. Trauma to articular chondrocytes induces apoptosis [33, 34] and apoptosis is mediated by an autocrine TNF pathway [35, 36]. Increased TGF-β activity in OA cartilage [37–39] causing down-modulation of the signalling IL-1RI [40] could in part compensate for the losses of IL-1RII caused by auto/paracrine TNF-α activity. If, however, druggable cytokine and growth factor pathways have to be identified, TNF-α and IL-1β and their signalling receptors are the main candidates (Fig. 1B).

Connective tissue structure-modifying agents (CTSMAs) and disease-modifying osteoarthritis drugs (DMOADs)
The first attempts at improving the structure and function of the connective tissues of synovial joints, thereby alleviating the symptoms of degenerative joint disorders, were based on vague assumptions that abundant administration of precursors of ECM components would help articular cartilage cells to replace the lost environment. This presumption prompted physicians to use substances such as glucosamine and sulphate or glycosaminoglycans aiming at improving cartilage repair in degenerative joint disease. Likewise, the first intra-articular administration of chondroitin polysulphate was based on the presumption that this heparinoid type of drug would replace hyaluronan as a lubricant and reduce fibrinogen levels in inflamed joints, and that this would produce a therapeutic advantage [41, 42]. Unexpectedly, some patients reported symptomatic relief after having undergone this procedure and even some changes in synovial fluid chemistry were reported [43].

Together with a profound search for mechanisms whereby joint tissues are destroyed in the course of inflammatory or degenerative joint diseases, researchers more methodically sought biological agents capable of restoring damaged connective tissues. As articular cartilage is one of the principal target tissues affected in the course of rheumatic joint disorders, many investigations focused on the metabolic characteristics of the single cell homing in this tissue: the chondrocyte. Substances that protected articular cartilage during the course of destructive joint disorders were termed chondroprotective agents. When this occurred in vitro in joints with osteoarthritis, these agents were termed disease-modifying osteoarthritis drugs (DMOADs) [1].

As the autocrine growth factor and cytokine cascades behind the development, homeostasis and destruction of the
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ECM of articular cartilage were not known previously, the first investigations on biological agents capable of modifying the structure of connective tissues in a positive way mainly concentrated on the ability of these agents to improve synthesis or to impair the degradation of ECM compounds, e.g. aggrecan and collagen. According to this definition, a number of substances could be classified as connective tissue structure-modifying agents (CTSMAs). Amongst these, sulphated glycosaminoglycans and glucosamine, chemically modified tetracyclines such as doxycycline and minocycline, diacetylglyceryl and its active metabolite rhein, and avocado/soybean unsaponifiables have been cited repeatedly.

Sulphated polysaccharides and chondroprotection

Among the first substances found capable of improving the accumulation of ECM compounds were the so-called chondro-mucopolysaccharides [44-46], a mixture of proteoglycan degradation products in which chondroitin sulphate was present. It was then hypothesized that chondroitin sulphate-containing ECM breakdown products somehow exerted positive feedback on articular cartilage chondrocytes. The possibility of interfering with connective tissue cell repair processes in vitro by sulphated polysaccharides was first described in the mid-1970s [47, 48]. Later, polsulphated chondroitin sulphate was shown to improve the synthesis of hyaluronan in synovial joints in vivo in human subjects [49]. The same drug, as well as its naturally occurring analogue, chondroitin sulphate, improved chondrocyte repair function in vivo in different experimental models of osteoarthritis [50–53]. Recently, randomized, double-blind, placebo-controlled therapeutic trials led to the conclusion that these CTSMAs had DMOAD properties, as they were shown to retard the progression of erosive OA in interphalangeal joint fingers [54, 55] and of OA of the knee in humans [56–58].

In vitro and in vivo experiments at various research centres concerning the effects on the metabolism of intercellular matrix molecules (proteoglycans, aggrecans, hyaluronan) have shown that most (poly)sulphated polysaccharides influence connective tissue cells (cartilage cells, synovial cells, fibroblasts) in a similar way [48, 59–61]. With the improvement of our insight into the auto-paracrine growth factor and cytokine pathways that control the homeostasis of healthy connective tissues, it became possible to study the mechanism of action of these CTSMAs. Recent investigations with sulphated polysaccharides showed that these agents operate in biological systems by the down-modulation of important catabolic auto-paracrine cytokine pathways, such as IL-1, thereby improving the accumulation of ECM compounds in the cell-associated matrix of these cells. Experiments with bovine cartilage cells obtained from macroscopically intact metacarpophalangeal joints showed that physiological concentrations of chondroitin sulphate significantly reduce downstream IL-1 effects such as collagenase, proteoglycanase and matrix metalloproteinase (MMP)-1 and MMP-3 activities [62]. Furthermore, chondroitin polysulphate inhibited the IL-1-induced mRNA expression of tissue plasminogen activator (tPA) [62]. Likewise, xylosan polysulphate and chondroitin polysulphate restored the accumulation of aggrecan, hyaluronan and type II collagen in the cell-associated matrix in IL-1β-treated human chondrocytes cultured in agarose. This effect probably resulted in part from the down-regulation of MMPs [63]. Also, in cultured equine chondrocytes chondroitin polysulphate significantly reduced IL-1β-enhanced expression of inducible nitric oxide synthase (iNOS) that was paralleled by increased release of NO. Chondroitin polysulphate reduced nitric oxide concentrations in the supernatants of these IL-1β-stimulated cultures [64]. Finally, a novel polsulphated polysaccharide, cyclodextrin polysulphate, showed cartilage structure-modifying effects in vitro as it improved the synthesis of aggrecan and the accumulation of cell-associated matrix macromolecules by human articular cartilage cells in alginate. Here, it was shown for the first time that this effect resulted in part from the direct repression of IL-1, as cyclodextrin polysulphate-treated cells expressed significantly lower amounts of intracellular IL-1α and β [65]. The same β-cyclodextrin-treated chondrocytes released significantly less IL-6 into the supernatant culture media, an effect known to result from auto-paracrine IL-1 stimulation [65].

Avocado/soybean unsaponifiables

Avocado/soybean unsaponifiables have been reported to repress chondrocyte catabolic activities and to increase the accumulation of proteoglycan by OA chondrocytes in culture. Avocado/soybean unsaponifiables were potent inhibitors of basal MMP-3 production by OA chondrocytes, and of the production of IL-6, IL-8, NO and prostaet in OA chondrocytes. Similarly, avocado/soybean unsaponifiables reversed the IL-1β effects in gingival fibroblasts from inflamed tissues [70]. The IL-1-repressing effects of these extracts protected subcutaneously implanted cartilage from degradation [71]. In vivo DMOAD effects following the administration of avocado/soybean unsaponifiables were reported in an ovine meniscectomy model of OA [72] and possibly in human OA of the hip [73].

Chemically modified tetracyclines

Chemically modified tetracyclines, such as doxycycline and minocycline, have been shown to directly inhibit protease and collagenase activities [74]. Tetracyclines may also indirectly suppress these catabolic activities as they were reported to decrease the levels of mRNA of collagenases in isolated OA chondrocytes. In addition, doxycycline inhibited the increase in mRNA for these enzymes in normal chondrocytes stimulated with TNF-α [75]. Likewise, chondrocytes isolated from human OA cartilage and treated with doxycycline showed significant inhibition of matrix metalloproteinase protein and corresponding mRNA levels, suggesting a transcriptional/post-transcriptional level of control. In addition, treatment with doxycycline resulted in a significant decrease in IL-1α and β and IL-6 mRNA [76].

The direct inhibition of such cytokines may have been responsible for the down-modulation of nitric oxide synthase activities in OA synovial cells [77]. Tetracyclines reversed both spontaneous and IL-1β-induced NOS activity in ex vivo conditions in human OA tissues. The mechanism of action of these drugs on NOS expression was found to be, at least in part, at the level of mRNA expression and translation of the enzyme [78].

It is plausible that the reduction of collagenase and gelatinase activities in extracts of human osteoarthritic cartilage after oral administration of these tetracyclines to humans [79], as well as the finding that doxycycline inhibits NO production in cartilage in dogs that developed OA after spontaneous anterior cruciate ligament rupture [80], may have been ascribed to the inhibition of auto-paracrine catabolic cytokine activities. Most probably, this inhibition of catabolic cytokine cascades was responsible for the 'chondroprotective' effects in inflammatory arthritides in animal models. Prophylactic doxycyclines and chemically modified variants given orally decreased OA changes in the knee joints in vivo in Hartley guinea-pigs, which have a high incidence.
of knee joint OA [81], and markedly reduced the severity of OA in weight-bearing regions of the medial femoral condyle in experimental OA in adult mongrel dogs [82]. More recently, treatment with doxycycline at 100 mg twice a day for 30 months was shown to slow down the rate of joint space narrowing in knees with established OA in a cohort of obese women [83].

**Diacetyl rhein**

In contrast to the other CTSMAs, which inhibit NO [64, 69, 77, 78, 107, 110–113] and the production of prostanooids [69, 108, 110–112, 114], the active metabolite of diacetyl rhein, rhein does not reduce but seems to stimulate prostaglandin synthesis *in vitro* [84, 85] and *in vivo* [86]. This mechanism of action of diacetyl rhein to augment the expression of cyclooxygenase (COX)-2 and PGE2 production, independent of their inhibition of endogenous NO [85, 87], is similar to that of tetracyclines, e.g., doxycycline and minocycline, which inhibit inducible NO synthase and augment COX-2 expression [88, 89]. Rhein and the tetracyclines are related chemical structures in that these compounds arise from substitution reactions of polynuclear hydrocarbons: anthracene and naphthacene, respectively. Rhein and tetracyclines possess structural similarities (Fig. 2).

Like the tetracyclines, diacetyl rhein/rhein repressed the expression of IL-1 in lipopolysaccharide-activated human OA chondrocytes [90] and synovial cells [91]. Experiments on isolated articular cartilage chondrocytes and on cartilage tissue explants revealed that this impaired release of active IL-1 was in part due to the inhibition of the plasma membrane IL-1-converting enzyme (ICE). Judging by the absence of effect on gene expression level of both proteins, the effect of diacetyl rhein/rhein on IL-18 and ICE was supposed to be post-translational [92].

Down-modulation of active IL-1 production was followed by inhibition of NFκB activation [93] and, consequently, the expression of IL-1/NFκB-dependent genes in these cells [90, 91, 93]. Blocking IL-1 downstream events included reduced production of NO, stromelysin-1 [91, 94] and collagenase, and of proinflammatory IL-6, -8 and -18 in IL-1α and TNF-α activated monolayer cultured human articular chondrocytes from OA joints [92, 94]. Likewise, rhein down-regulated the IL-1-induced gene expression of proMMP-1, -3, -9 and -13 and their activities and up-regulated production of tissue inhibitor of metalloproteinase 1 (TIMP-1) in monolayer cultured rabbit articular chondrocytes. Therefore, increased production of glycosaminoglycans and collagen along with decreased degradation of proteoglycan was reported in these cells [95–97]. This improved matrix build-up may have been enhanced by increased expression of TGF-β isomers in chondrocytes treated with diacetyl rhein [98]. All these *in vitro* results were obtained with diacetyl rhein/rhein concentrations comparable to therapeutic plasma levels. It can be reasonably anticipated that IL-1-blocking by diacetyl rhein/rhein was responsible for some of the DMOAD effects observed in experimental OA in animals, e.g., in contusion-induced cartilage destruction of the rabbit patella [99] and in spontaneously developing polyarthritis in NZB/KN mice [100]. Although not concuring with improved articular cartilage biochemistry [101–103], comparable chondroprotection was observed in different canine OA models when judged on macroscopical cartilage lesions [102, 103].

These DMOAD effects have been confirmed in two randomized, double-blind, placebo-controlled studies. Two hundred and sixty-nine patients with primary OA of the hip finished a 3-yr study whilst receiving diacetyl rhein, 50 mg twice a day, or placebo. The percentage of patients with radiographic progression, defined as a joint space loss of at least 0.5 mm, was significantly lower in patients receiving diacetyl rhein than in patients receiving placebo. In these patients the rate of joint space narrowing was directly, though significantly, lower than in the placebo group [104]. These results were confirmed in another 1-yr prospective, randomized, double-blind, placebo-controlled study of 301 patients with radiological medial knee OA [105].

**Glucosamine**

The place of glucosamine as a CTSM or DMOAD remains controversial. The fact that this amino sugar has for a long time been termed ‘glucosamine sulphate’ has generated confusion. The preparation used in a number of *in vitro* and *in vivo* experiments was not a glucosamine sulphate ester but happened to be a preparation in which glucosamine and sulphate occurred as two single molecules in crystalline form. If any CTSM effects are ascribed to ‘glucosamine sulphate’, it is currently accepted that the monosaccharide is the active ingredient. In a series of experiments on isolated IL-1α-activated chondrocytes in culture where hexosamines have been used, effects on IL-1 downstream events have been reported. Addition of glucosamine to rat chondrocytes treated with IL-1α decreased the activation of the transcription factor NFκB, but not the activator protein-1 [106]. Glucosamine, but not N-acetyl glucosamine or other monosaccharides [107], significantly inhibited NFκB activity in human OA chondrocytes, as well as the nuclear translocation of p50 and p65 proteins [108]. Glucosamine reduced phospholipase A2 activity [109], COX-2 mRNA and protein levels [107, 108, 110] and PGE2 release [108, 110–114] in articular cartilage cells of different origin. Likewise, the amino sugar downgraded chondrocyte iNOS and NO production [107, 110–113] and IL-1-induced metalloproteinase and collagenase activities in chondrocyte culture supernatants [109–113, 115]. Marked inhibition of aggrecanase-dependent cleavage of aggrecan was observed with both rat cells and bovine explants when supplemented with glucosamine [116] and mansosamine [117]. Inhibition was not due to interference with IL-1 signalling, and the precise mechanism by which hexosamines function in this system is unclear. Interference with enzyme activities resulted in a decrease in ECM catabolism in these chondrocyte cultures [113]. Additionally, hexosamines were reported to improve the synthesis of ECM macromolecules in IL-1-repressed cartilage cells [106, 111, 112, 115]. Most cited experiments were conducted on IL-1-primed normal or OA chondrocytes or cartilage explants.

![Fig. 2. Rhein, the active metabolite of diacetyl rhein, and tetracycline possess structural similarities.](https://academic.oup.com/rheumatology/article/45/2/129/1784540)
Rarely, native OA chondrocytes were used [109, 115]. The major problem with the in vitro studies done so far are the concentrations of the hexosamines used in these experiments. Routinely, 1500 mg of glucosamine (20 mg/kg in a 75 kg subject) is administered daily in patients with OA. These prescribed amounts at the most ensure plasma concentrations of 0.15–0.30 mM of the hexosamine in an average Caucasian. Two of the above-mentioned experimental studies were conducted with glucosamine concentrations within this range [115, 117]. The remainder were done using non-physiological nutrient medium glucosamine levels ranging between 0.56 and 139.66 mM [106–113, 116], conditions in which the inhibition of the catabolic effects induced by IL1β might have been related to glucosamine toxicity [118].

The relevance of the in vitro results obtained with supraphysiological doses of glucosamine remains contentious as daily administration of ~20 mg/kg of glucosamine by the oral route in rabbits in which anterior cruciate ligament transection was performed had only a detectable, site-specific, partial disease-modifying effect in this model of OA. The administration of glucosamine did not prevent fibrillation and/or erosions of the articular cartilage in the treated animals [119]. Also, parenteral administration of 200 mg/kg of N-acetyl-glucosamine in a rabbit model of experimental knee OA did not show chondroprotective effects [120]. The mechanism of action by which this hexosamine thus might have affected the evolution of one human population with OA of the knee [121, 122] thus remains to be elucidated. Considering the absence of chondro-protection in experimental animal models of OA, confirmation of the chondroprotective effects of glucosamine in a human population would be of value.

Corticosteroids and IL-1

Homeostasis of the ECM by articular cartilage cells depends on the control of the auto/paracrine IL-1-induced catabolic cascades [21]. A multitude of endocrine hormones and growth factors are capable of controlling this IL-1 activity. Corticosteroids have been classically reported to directly interfere with IL-1 synthesis [123, 124]. As shown in cartilage explant cultures, corticosteroid hormones at physiological doses have been shown to inhibit the degradation of the ECM [125–127]. This inhibition of the IL-1 pathway resulted in a reduction of pathological neutral protease activities in cartilage tissue [128–132]. Aside from the fact that corticosteroids act synergistically with different essential growth and differentiation factors to affect the synthesis of the ECM ground substance [133–135], the anticytotoxic effects of corticosteroids at least in part explain the protective effects on OA cartilage of single or intermittent local or systemic administration of physiological doses of corticosteroids in different models of experimentally induced OA, such as the meniscectomized rabbit model [136, 137], in chemically induced cartilage damage in the guinea-pig [138] and in the Pound-Nuki dog model of OA [132, 139]. Similar protective effects of these drugs were observed on OA cartilage of human patients [131]. This repression of IL-1 by physiological doses of corticosteroids, together with the up-regulation of the receptor for IGF-1, eventually resulted in the accumulation of ECM compounds in the immediate environment of cartilage cells in vitro [63, 140].

Protection and regeneration of articular cartilage by cytokine blockers: proof of concept

More recently, dramatic chondroprotective effects have been documented in patients with RA and in the spondyloarthropathy (SPA)-associated forms of destructive arthritis. In these patients, TNF-α released in the synovial membrane sets off the catabolic auto/paracrine IL-1 pathway of chondrocytes in the adjacent articular cartilage [141]. The resulting auto/paracrine IL-1 cascade will induce destruction of the ECM of articular cartilage. Treatment of RA patients with TNF-α-scavenging recombinant proteins represses this chondrocyte IL-1 activity and halts the erosive progression ongoing during the course of these inflammatory diseases [142]. Neutralizing TNF-α in RA eventually resulted in obvious repair in the affected joints [143]. Reappearance of a joint space that had disappeared has been documented in peripheral arthritis associated with SPA [144, 145] (Fig. 3). Similarly, in OA, auto/paracrine TNF-α resulting from apoptosis of chondrocytes [31–34] following excessive mechanical stress induces an IL-1-induced destruction of the extracellular environment of articular cartilage. How far similar TNF-α blocking can result in halting the progression of this disease has not yet been explored.

Fig. 3. Chondroprotection and regeneration of articular cartilage by cytokine blockers. (A) Hip joint of a patient with ankylosing spondylitis before (left) and after 1 yr of treatment with the TNF-α blocking monoclonal antibody infliximab. Erosive progression has been ended and joint space reappeared. (B) The same course was seen in a third proximal interphalangeal and a second distal interphalangeal joint of a patient suffering from psoriatic arthritis. These records were obtained after the completion of a series of prospective, randomized, placebo-controlled trials, approved by the local ethics committee, in which a total of 107 patients were included to study the effects of infliximab on the clinical features of spondyloarthropathy [144, Van der Bosch, submitted]. X-rays of the affected joints were taken at entry and after 1 yr of follow-up. (C) In erosive interphalangeal finger joint OA, a similar type of remodelling occurs spontaneously after halting of a destructive episode. The four X-rays were taken at 1-yr intervals [145].
Discussion

Identical cytokine and growth factor pathways are in control of destruction and repair in OA and in inflammatory joint diseases such as RA and SPA-associated arthritis. Unidirectional TNF-α/IL-1-driven cytokine cascades disturb the homeostasis of the ECM of articular cartilage in these disorders. Synovial membrane-derived TNF-α triggers the cascade during inflammatory pathologies, whilst in OA autocrine TNF-α released by apoptotic articular cartilage cells sets off IL-1 activity. Both in inflammatory and in degenerative conditions, the TNF-α/IL-1-driven cytokine cascades overrun the anabolic repair-promoting growth factor pathways. However, when TNF-α-blocking biologics have been administered in the immunologically mediated inflammatory arthritides, tissue repair has been demonstrated unmistakably. Reappearance of a joint space that had disappeared before has been documented in SPA.

Likewise, repression of TNF-α/IL-1-driven cytokine cascades should allow repair to become even more obvious in OA as anabolic growth factor pathways are also overexpressed in this condition. Corticosteroids, select classes of (poly)sulphated polysaccharides, tetracyclines, diacetylrhein/rhein, avocado/soybean unsaponifiables and glucosamine have been shown to inhibit the expression of iNOS and the increased release of PGE2, IL-6 and IL-8. Except for glucosamine, promotion of growth factor pathways. However, when TNF-α-blocking biologics have been administered in the immunologically mediated inflammatory arthritides, tissue repair has been demonstrated unmistakably. Reappearance of a joint space that had disappeared before has been documented in SPA.

As the unidirectional TNF-α/IL-1-driven cytokine cascade has been identified as a druggable target in OA, simple laboratory procedures will allow new series of CTSMAs with DMOAD activity to be discovered.

The authors have declared no conflicts of interest.

References


