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ORIGINAL STUDY

Current status of anti-inflammatory therapy for posttraumatic osteoarthritis

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Although there is ample evidence that intra-articular injuries are associated with the up-regulation of pro-inflammatory cytokines, the success of anti-inflammatory, disease-modifying treatments to prevent posttraumatic osteoarthritis (PTOA) remain uncertain.

To summarize the current status of anti-inflammatory therapy for PTOA, we conducted a systematic review.

9 clinical studies in humans were identified applying anti-inflammatory agents to prevent or treat PTOA. A total of 347 patients aged an average 41 ± 14 years were included in this review. 5 studies had comparable designs with randomized allocation. Those studies of course had a statistically significant higher Coleman Methodology Score (65 ± 6) than the case-control studies (39 ± 13, p = 0.013). The most frequently reported main outcome parameter was pain assessed by different scales (n = 7), the most examined joint the knee (n = 7). The majority of the analyses (n = 6) focused on the intra-articular (IA) application of hyaluronic acid (HA) reporting mainly positive effects. One study stated positive results following IA administration of Interleukin 1 receptor antagonist in patients presenting rupture of the anterior cruciate ligament. Platelet-rich plasma was also used to relieve symptoms following acute injury, but the study quality was too low to conclude any effects.

Although the initial data, especially regarding IA HA injection, are encouraging, study designs differ substantially. Therefore, current data does not allow us to conclude that anti-inflammatory therapy following acute injuries has beneficial effects on short- or long-term outcomes.

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Keywords : systematic review ; anti-inflammatory ; therapy ; posttraumatic ; osteoarthritis.

INTRODUCTION

Regarding the quality of life, physical impairment caused by osteoarthritis (OA) of a single lower extremity joint equals that caused by end-stage kidney disease or heart failure (*11*). The clinical impact associated with joint degeneration due to osteoarthritis/osteoarthrosis has turned the disease into a world-wide epidemic causing an economic catastrophe to insurance companies and ample financial gains for the arthroplasty industry. Current treatment modalities for the young tend to treat the symptoms rather than the causes, contrary to the tenets of modern medicine. The numbers of total

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joint replacements are constantly rising despite significant limitations and the potential complications such patients are subject to. There is thus broad consensus about the need to develop disease-modifying treatments for osteoarthritis (OA) through studies of cohorts suffering from injuries involving the high risk of OA development, particularly when young human subjects with acute ligament injuries (*16*) and fractures (*70*) are affected. Despite sufficient restoration of biomechanical stability and joint congruency accomplished by reconstructing the anterior cruciate ligament (ACL) or by fracture reduction, the risk of ongoing articular degeneration remains high (*54,66*). Animal studies and human trials have demonstrated the induction of a pro-inflammatory cascade triggered by acute injuries, suggesting that inhibiting inflammation might inhibit OA development (*52*). We carried out this systematic review to summarize the current knowledge of anti-inflammatory therapy in treating posttraumatic osteoarthritis, hypothesizing that we would detect substantial evidence for clinical applications. Before studies were included in the review, the molecular justifications for anti-inflammatory effects were verified by a literature search. Particularly when multiple effects were described, done for example regarding hyaluronic acid (HA) or platelet-rich plasma (PRP), trials were included only when evidence was presented describing specific anti-inflammatory characteristics.

METHODS

For this systematic review, a literature search was conducted to identify any published clinical studies on anti-inflammatory therapy for posttraumatic osteoarthritis by including the following databases : MEDLINE and MEDLINE preprints (836), Life Science Citations (+22), British National Library of Health (+0), Cochrane Library (+29), DIMDI (including BIOSIS, Deutsches Ärzteblatt, EMBASE Alert, EMBASE, gms, gms Meetings, SciSearch) (+208). The literature search period started on 1/1/1948. To develop a search strategy, we applied the following terms (including reasonable abbreviations) associated consecutively with each other : osteoarthritis (PTOA[tiab], "Posttraumatic Osteoarthritis"[tiab], Osteoarthritis[tiab], "Osteoarthri-tis"[Mesh], "Arthritis"[Mesh :noexp]), anti-inflammatory (inflam*[tiab], antiinflam*[tiab], anti-inflam*[tiab], "Anti-Inflammatory Agents"[Mesh]), Cochrane Filter RCTs, injury/trauma ("Fractures, Bone"[Mesh], fracture*[tiab], injur*[tiab], trauma*[tiab], posttrauma*[tiab], acute*[tiab]. This resulted in the following term that was used searching the MEDLINE database : ((((("Arthritis"[Mesh :noexp]) OR ("Osteoarthritis"[Mesh]) OR (Osteoarthritis[tiab]) OR ("Posttraumatic Osteoarthritis"[tiab]) OR (PTOA[tiab])) AND (("Anti-Inflammatory Agents"[Mesh]) OR (anti-inflam*[tiab]) OR (antiinflam*[tiab]) OR (inflam*[tiab]))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT 24)) AND ((acute*[tiab]) OR (posttrauma*[tiab]) OR (trauma*[tiab]) OR (injur*[tiab]) OR (fracture*[tiab]) OR ("Fractures, Bone"[Mesh])). This resulted in 832 hits on 7/29/2014, which was reproducible on 8/26/2014 with 836 hits. The following search strategy was used for the DIMDI search surface : (AU = OSTEOARTHRITIS ? OR (OSTEOARTHRITI#)) AND (AU = CLINICAL TRIAL ? OR (CLINIC### AND TRIAL#)) AND ANTI# AND INFLAMMATOR%## AND POSTTRAUMAT### and (AU = OSTEOARTHRITIS ? OR (OSTEOARTHRITI#)) AND (AU = CLINICAL TRIAL ? OR (CLINIC### AND TRIAL#)) AND ANTI# AND INFLAMMATOR%## AND INJURY#. The retrieved reviews were scanned for further articles, and relevant studies were also included in the review (+17). The quality of each study included in the review was evaluated using the Coleman Methodology Score (CMS) (*17*). The numbers of the articles found and included in the systematic analysis are shown in figure 1 according to the PRISMA guidelines (*58*). All studies were excluded that examined cartilage repair procedures, biomarker profiles, any form of bracing, application of an orthosis or surgical procedures, and exclusively analgesic treatment in acute, posttraumatic OA. Studies addressing physiotherapy were also excluded. Exercise has been shown to exhibit anti-inflammatory effects (*31*), however, considering how multifactorial treatment that approach is, we found its effect to be of subordinate importance and therefore excluded the item "exercise" from this review. Furthermore, investigations not performed in humans or done in patients with exclusively rheumatoid arthritis (RA), goat or any form of chronic OA were excluded. Moreover, we limited the review to joints of the extremities. The search, selection of articles, and evaluation were done by two investigators (HS and GMS). The clinical trial registries ClinicalTrials.gov and WHO ICTRP were searched

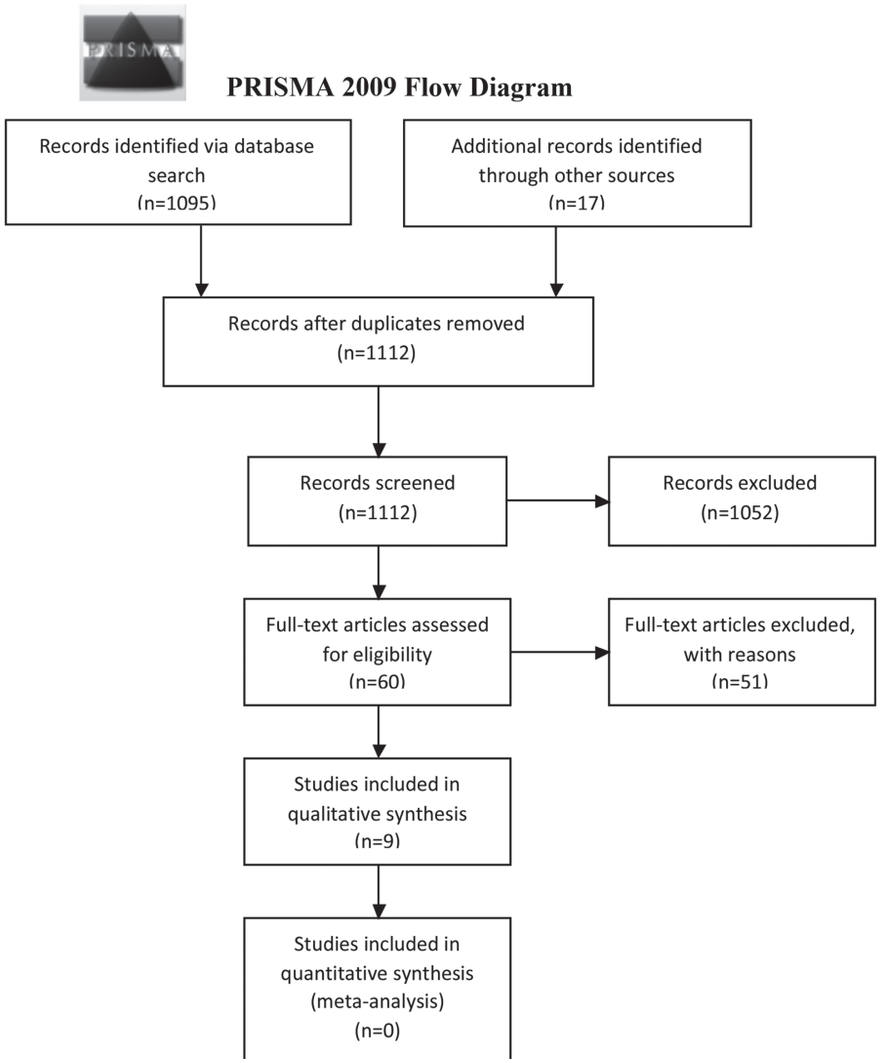

Fig. 1. — The flow chart illustrates the number of articles identified that included systematic analysis according to PRISMA guidelines.

applying the terms "Osteoarthritis AND anti-inflammatory" and "prevent AND osteoarthritis", resulting in 392 hits.

RESULTS

9 clinical studies in humans were identified applying anti-inflammatory agents to prevent or treat PTOA (*10*,*33*,*48*,*56*,*67*,*75*,*79*,*81*,*83*). The concept of pain-relieving effects of anti-inflammatory drugs applied for acute injuries goes back to 1966 (*75*). A total of 347 patients with an average age of 41 ± 14 years were included in this review. 5 studies were similar in design with randomized allocation. Unsurprisingly, the randomized controlled studies (RCT) had a statistically significant higher CMS (65 ± 6) than the case-control studies (39 ± 13, $p = 0.013$). The trials mainly focused on the knee (n = 6), but ankle (n = 1) and elbow (n = 1) were also joints of interest. The injuries included were very heterogeneous and included specific diagnoses such as ACL tears (*33*,*48*), ankle fractures (*79*) and

unspecific descriptions including fractures, sprains, contusions or just acute knee injury. We also identified studies focusing more on PTOA, which included patients suffering from primary or secondary OA (*67*), early OA with secondary damage (*81*) or just PTOA (*10*). Although the time period between injury and application of the anti-inflammatory medication can decisively influence outcomes, only 3 studies reported that parameter at all. One can assume a 2-week interval in case of fractures (*79*), the duration allocated for one trial recruiting patients with acute ACL tear (*48*). Two studies reported minimal periods of 20 days (*56*) or 3 months (*67*) between the actual trauma event and earliest treatment application. Only one trial reported outcome assessments after more than one year (*79*) ; all other studies focused on short-term results between 2 weeks and one year. The most frequently reported main outcome parameter was pain assessed by different scales (n = 7). Most of the studies combined this with objective measurements of range of motion (n = 4) or established scores (n = 5). The majority of the analyses (n = 6) investigating the effect of anti-inflammatory agents on posttraumatic OA focused on the intra-articular application of hyaluronic acid (HA). 4 research papers reported positive effects, and one no influence on clinical outcome by it. Although another trial only examined follow-ups without comparison to a control cohort, the application of HA in acutely-injured patients seems to be beneficial, considering that 4 reports applied an RCT design with a CMS ≥ 60. Unfortunately, the clinical indication, the algorithm of application, the applied medical product and outcome parameters differ substantially, making any statistical analysis beyond description impossible. Besides HA, Interleukin-1 receptor antagonist (Anakinra®) was administered in one clinical trial's set-up (*48*). This is a substance belonging to the group of biologicals primarily developed to treat rheumatoid arthritis (RA). Systematic reviews have demonstrated the efficacy of Anakinra® in treating RA (*61*), however, the study by Kraus *et al* was the first trial testing its potency following acute injury. One single-center, uncontrolled, prospective preliminary trial using PRP to treat secondary knee OA was included in the review, showing positive effects on pain and Knee Injury and Osteoarthritis Outcome Scores (KOOS) (*67*). Unfortunately, that study combined primary and secondary OA and recruited very few patients. Considering the overall low quality of that study's design (resulting in a CMS of 45 points), their data do not allow us to conclude that PRP exhibits positive effects after knee injuries. Although many of the retrieved publications investigated the effect of non-steroidal anti-inflammatory drugs (NSAID) (*3*,*22*,*30*,*40*,*49*,*73*,*74*), we identified no study that specifically recruited patients with posttraumatic osteoarthritis. The main focus of these investigations was on OA without further specification, RA, primary OA or soft-tissue trauma (*69*,*82*). Both oral and percutaneous applications (*21*,*26*) have been reported. Intra-articular glucocorticoid injection (*14*,*19*,*25*,*80*) is obviously associated with anti-inflammatory effects, however (resembling NSAIDs indications), it comprised only chronic inflammatory joint diseases such as goat or RA. The only study we found explicitly aiming to treat acute joint injuries using orally-applied glucocorticoids was performed in 1966 using a combined approach with pain medication and vitamin B complex (*75*). Although the idea of simultaneously inhibiting inflammation and pain seems appealing, the medication used for that trial in 1966 is no longer in use, since propoxyphene was taken off the European market because of its hepatotoxicity (*5*). We detected only one ongoing trial evaluating anti-inflammatory effects on acute injury (*51*). The MOON-AAA GCP clinical trial is investigating the effect of Kenalog®, an intra-articularly injected glucocorticoid, on outcome following ACL tear and is still recruiting patients. The sequential injections start within one week following injury.

DISCUSSION

Our review's main finding is that the principle of anti-inflammatory therapy to prevent posttraumatic OA has been successfully applied in a variety of patients via the intra-articular (IA) administration of hyaluronic acid (HA) and IL-1 receptor antagonist. Although the initial evidence, especially regarding IA HA injection, is encouraging, the study designs differ substantially in terms of clinical indication,

Table I. — Parameters for defining the quality of and specifying the identified studies; PMID : Pubmed identification ; CMS : Coleman Methodology Score ; PTOA : posttraumatic osteoarthritis ; RCT : randomized controlled trial

PMID/Journal	Authors	Year	CMS	N total	N with intervention	Study design	Specifically PTOA	Exclusively PTOA
22273632	Kraus *et al*	2012	66	11	6	RCT	yes	yes
21403592	Sampson *et al*	2010	45	14	14	Case control	no	no
20145786	Westrich *et al*	2009	62	46	no info	RCT	yes	no
17620776	Huang *et al*	2007	75	120	90	RCT	yes	yes
17084297	Brakel *et al*	2006	53	19	19	Case control	yes	yes
11826644	Wang *et al*	2002	35	37	37	Case control	yes	yes
Clinical Drug Investigation	Di Marco *et al*	1995	60	30	15	RCT	yes	yes
European Journal of Rheumatology and Inflammation	Zattoni *et al*	1995	62	50	24	RCT	yes	yes
6013741	Sixt *et al*	1966	24	20	20	Case control	yes	no

the joint affected, algorithm of application, medical product applied, the interval between injury and application, and outcome parameters. Therefore, current data does not allow us to conclude that anti-inflammatory therapy following acute injuries exerts beneficial effects on short-term outcome. Considering the generally very brief follow-up periods that have been reported, long-term effects such as the desirable prevention of PTOA are still in doubt.

The role of inflammation in the context of regenerative musculoskeletal medicine is a subject of growing importance since it is now acknowledged to be a major factor in preventing the onset or progression of OA (*12*,*60*,*65*). It remains controversial whether joint degeneration, e.g. that following rupture of the anterior cruciate ligament (usually biomechanically unstable, or usually chronic and inflammatory following a fracture/cartilage defect) can be considered osteoarthrosis without an inflammatory component, or rather osteoarthritis with an inflammatory component, or both (*29*). The overall trend revealed in the available data suggests that inflammation is much more likely in most cases. Interestingly, different artificial degenerative joint rat models following meniscus tear, ACL transection or IL-1β administration produced different joint destruction patterns (*1*,*9*,*38*). This is in light of the fact that not one compound within the joint causes an inflammatory milieu, but a cocktail of different factors that probably do not act out fully at the same time. Nevertheless, one irrefutable morphological contact point in OA development is the pathological change in articular cartilage triggered by pro-inflammatory cascades. In this context it has to be pointed out that there is an enormous difference between chronic OA and chronic inflammatory arthritis such as RA, two fundamentally different forms of the disease process. This review excluded all studies that described inflammatory pathways as an onset of OA and focused on the posttraumatic pathogenesis. Nevertheless, there are partially redundant regulatory biochemical mechanisms.

Hyaloronic acid to prevent PTOA

HA application is usually summarized as viscosupplementation because HA is a glycosaminoglycan providing joint lubrication and shock absorbency and acting as the backbone for proteoglycans in the extracellular matrix (*77*). Beyond these biomechanical effects, an *in-vitro* study demonstrated convincingly that HA inhibits IL-1β-induced MMP-13 via its principal receptor, CD44, and subsequent intracellular p38 MAPK signaling in OA and RA chondrocytes (*41*). Furthermore, CD44 expression seems to be associated with synovial catabolic conditions as observed in acute and chronic forms of OA (*71*). Considering the additional function of HA

Table II. — Parameters examined in the identified studies ; ACL : anterior cruciate ligament ; OA : osteoarthritis ; IL1RA : Interleukin 1 receptor antagonist ; IA - intra-articular ; no info. : no information provided ; VAS : visual analog scale ; KOOS - Knee Injury and Osteoarthritis Outcome Scores ; ADL : activities of daily life ; HA : hyaluronic acid ; PRP : platelet-rich plasma

Authors	Joint	Injury	Duration	Follow-up	Mechanism	Application	Outcome Parameter	Effect	Age (years)
Kraus *et al*	knee	ACL tear	14 days	14 days	IL-1RA	IA	Pain VAS KOOS	positive	24
Sampson *et al*	knee	Primary and secondary OA	> 3months	52 weeks	PRP	IA	Pain VAS KOOS	positive	52
Westrich *et al*	knee	Early OA in combination with a symptomatic meniscus tear	no info.	6 months	HA	IA	Pain VAS Swelling Effusion Range of Motion	positive	59
Huang *et al*	knee	ACL tear	no info.	12 months	HA	IA	Lysholm knee scoring scale Knee range of motion Ambulation speed Muscle peak torque (MPT) of knee flexion and extension	positive	27
Brakel *et al*	elbow	PTOA without further details	no info.	6 months	HA	IA	Pain VAS Elbow Function Assessment Score Functional Rating Index of Broberg and Morrey Modified Andrews Elbow Scoring System	no	46
Wang *et al*	ankle	Ankle fracture	no info.	27 months	HA	IA	Pain VAS Walking ADL	no comparison	no info
Di Marco *et al*	knee	Intra- and extraarticular fractures, Acute knee injury, Ligament tear with reconstruction	≥20days	45 days	HA	IA	Pain VAS Range of Motion	positive	38
Zattoni *et al*	knee	Acute knee injury	no info.	58 days	HA	IA	Pain VAS Range of Motion Lysholm knee scoring scale	positive	no info
Sixt *et al*	no info.	Fractures, sprains, contusions of various joints	no info.	4 months	combination of prednisolone, propoxyphene, vitamin B complex	oral	Subjective reports of patients	positive	no info

as a scavenger for different radicals (*68*), anti-inflammatory effects are associated with the administration of HA inhibiting different pro-inflammatory pathways. Although HA effects cover a whole spectrum of different action modes, we have included the substance class in this review for their substantial anti-inflammatory components. For intra-articular (IA) injection, various HA preparations are

available that differ in molecular weight, production method, dosing, and biologic characteristics, but clinical trials to date have failed to provide evidence of any one product's benefit (*18*). But it appears that HA preparations with a molecular weight < 500 kDa are ineffective to reduce pain and improve function because of weak binding to the cell-surface receptor (*23*). The effect of HA application was reviewed in 2006 by Bellamy *et al*, who demonstrated beneficial effects on pain, function, and patient global assessment especially at the 5-to-13-week post-injection period in knee OA (*6*). Studies conducted since the Cochrane review was published are summarized by Kon *et al* (*45*) showing consistent positive effects in all stages of chronic OA. Considering anti-inflammatory properties, one non-inferiority study showed that the efficacy of IA-HA injection is similar to NSAIDs', and that the safety profile is even superior to that of NSAIDs in patients with knee OA (*37*). The majority of clinical trials included in this review support the idea that IA HA application reduces pain not only in chronic stage OA, but that it exhibits positive short-term effects on injured joints as well, exerting a potentially positive influence on OA development.

Inhibition of pro-inflammatory cascades to prevent PTOA

A new approach to prevent PTOA is to administer biologicals, which are widely used to treat chronic forms of OA via autoimmune pathological pathways such as RA. The most important enzymes involved in cartilage destruction are the family of zinc-dependent matrix metalloproteinases (MMPs). Proteins of the MMP family are involved in the breakdown of extracellular matrix in normal physiological processes, e.g. in embryonic development, reproduction, tissue remodeling as well as in disease processes such as arthritis and metastasis. *In-vitro* studies suggest that IL-1 causes cartilage destruction by stimulating the release of MMPs and other degrading metabolites. Interleukin-1 receptor antagonist (IL-1RA) as a member of the IL-1 family binds to IL-1 receptors, but induces no intracellular response. IL-1RA prevents interaction between IL-1 and its cell surface receptors, and thus competitively inhibits the biological effects of IL-1 (*2*). Human articular chondrocytes produce soluble IL-1RA (sIL-1RA) in response to IL-1β and IL-6. This effect reflects increased transcription from the sIL-1RA promoter. The local production of sIL-1RA in cartilage may have a protective effect against articular inflammatory and catabolic responses (*64*). Literature data on IL-1β are conflicting. Kerkhof and co-workers recently published intriguing data from their large-scale meta-analysis of IL-1β and IL-1RA polymorphisms contributing to the risk of radiographic hip and knee osteoarthritis and the severity of knee osteoarthritis. They postulate that a common genetic variation in the IL-1 region is not associated with the prevalence of hip or knee OA, while a variation of IL-1RA might play a role in the severity of knee OA (*43*). Kobayashi and co-workers have added antagonists of IL-1 and TNFα to explant cultures of non-arthritic and OA articular cartilage. Their research group discovered that the antagonists inhibited the increase in collagen type II cleavage by collagenase as well as the increase in GAG release observed in OA cartilage compared with normal cartilage. Kobayashi *et al* also reported that inhibition was significant in tissue from some patients but not others. They point out the fact that IL-1β and antagonistic effects are heterogeneous and may very well be species-specific also, as reported previously (*76*). These results suggest that the autocrine/paracrine activities of TNFα and IL-1 in articular cartilage may play important roles in cartilage matrix degradation in OA patients, however, this effect exhibits individual variability (*44*). Varying outcomes following IL-1β application may be related to different cytokine concentrations, culture modes and models, culture times, OA and non-OA chondrocytes as well as differing species. Chondrocytes in OA cartilage, especially those in clonal clusters, express receptors reacting to cytokines and chemokines produced in the synovium (and other peri-articular joint tissues), which have been detected in osteoarthritis synovial fluid. Thus, IL-1β mRNA may be induced in chondrocytes, and the inflammasome complex, but active IL-1β is not produced and secreted by OA chondrocytes, which suggests that cartilage may be degraded independently of inflammasome activity. Following that

thought, Hauselmann and co-workers reported that cartilage damage in arthritis occurs initially in the superficial layers. Interestingly, chondrocytes isolated from these regions appear to be more susceptible to IL-1 than those found in deeper layers. When chondrocytes from the superficial and deeper layers were cultured and stimulated with IL-1, greater release of MMPs and greater inhibition of proteoglycan synthesis were observed in superficial chondrocytes. Notably, IL-1RA was more effective in blocking the detrimental effects of IL-1 in the deeper layers, presumably due to their lower concentration of IL-1 receptors. Hauselmann's group applied human chondrocytes in their study (*27*). Neidhart cultured human and bovine chondrocytes in sponges, added RA synovial fibroblasts and modulated the system by adding monocytes, IL-1β, TNFα, IL-1RA and monoclonal antibodies against IL-1β and CD44. They discovered extensive matrix- and cell-destructive effects through fibroblasts that could be increased by adding the mentioned pro-inflammatory cytokines, whereas IL-1RA and anti–IL-1β monoclonal antibodies reduced the destruction of human matrix by 45% and 35%, respectively (*63*). Allen and co-workers reported that adding recombinant IL-1RA had no effect on IL-1β-mediated allodynia and cartilage loss in a rat knee model, speculating that rapid joint clearance of IL1-RA might have been responsible for this failure (*1*). It has been reported that deletion of the IL-1RA gene leads to the spontaneous development of chronic polyarthropathy in BALBu cA mice. The incidence of arthritis was 80% at 8 weeks of age and 100% at 16 weeks of age, with signs of inflammation being more pronounced in hind limbs than in the front paws. Their polyarthritis was pathologically characterized by synovial hyperplasia, leucocyte infiltration and erosive pannus formation. IL-1β levels were 10-fold higher in the IL-1RA-deficient animals than in controls, with TNFα levels only slightly increased (*32*). The literature specifies that an extreme excess of IL-1RA is required to block IL-1β actions. IL-1RA production was assessed in culture supernatants and lysates of chondrocytes incubated with various cytokines. Similar results were obtained with freshly isolated chondrocytes and subcultured cells after one to seven passages. IL-1RA was undetectable in supernatants of untreated cells, but IL-1β stimulated its production (*59*). Kraus and group were the first to report human data on the use of IA application of IL-1RA. Although such results (*48*) using Anakinra® appear encouraging, the trial's obvious weaknesses, very brief follow-up period, and small study cohort detract from its value. The current evidence does not allow us to generalize regarding positive effects on pain relief and specific function, but will soon lead to the question as to whether other anti-inflammatory drugs with a spectrum of applications comparable to Adalimumab® or neutralizing TNFα may be tested in the prevention of PTOA. In any case, the intra-articular application of neutralizing antibodies is controversial. Bokarewa *et al* (*8*) report on the local infusion of infliximab to treat acute joint inflammation. Their results reveal that effects of intra-articular treatment with TNFα antagonists are comparable with those of corticosteroid injections. The authors argue that the amount of infusion of the antibodies was insufficient to bind the large amount of cytokines present in the joint. Furthermore, antibodies probably do not penetrate the synovial tissue or act on intracellular protein pools. It is also possible that immune complexes induce TNFα effects and cause inflammatory cascades via the Fc-receptor (*7*). Moreover, one specific antibody may only neutralize a single component in a partially-redundant cascade of inflammation. Based on the facts presented above, one would assume potentially positive effects of glucocorticosteroids applied intra-articularly and inhibiting a whole spectrum of inflammatory cascades. However, the value of IA steroids in the symptomatic treatment of OA with acute exacerbations or to prevent posttraumatic joint degeneration has not been adequately assessed (*24*).

PRP for prevention of PTOA

The idea that PRP exhibits anti-inflammatory properties is mainly based on investigations done with Orthokine® (*4*), because IL-1RA is known to be present at Orthokine® at higher concentrations than in serum. However, PRP is a drug that has not been specified, and its composition varies depending on preparation procedures, storage and applica-

tion modalities, platelet counts, possible addition of white blood cells, concentration rates, and optional activation methods. This results in great uncertainty about possible effects and makes it difficult to compare studies. Despite these problems, there have been a huge number of clinical trials performed and published investigating possible effects of PRP in a variety of orthopedic diseases. The postulated mechanisms of action are usually either of anti-inflammatory or regenerative nature and reasoned by the presence of specific growth factors or cytokines with inhibiting impacts on inflammatory cascades. Effects in OA treatment were reviewed very competently by Kon *et al* (*46*), who showed that based on current evidence, PRP treatment should only be indicated for low-grade cartilage degeneration and when traditional conservative approaches have failed. Furthermore, most of the studies we identified aimed to treat primary OA, not secondary or even specifically posttraumatic OA. The only trial we identified that included patients with the latter conditions was carried out by Sampson *et al* (*67*). As their study design entailed a poorly-specified intervention cohort and very few patients, PRP application in PTOA cannot be recommended. This finding falls in line with the conclusion drawn in the aforementioned review by Kon *et al* (*46*) regarding OA treatment in general.

Further opportunities

Further key pathways to prevent PTOA were recently summarized by Chubinskaya *et al* (*15*). Treatment with antioxidants (*57*), apoptosis inhibition (*35*), and the protection of cell membrane integrity (*36*) have been suggested for chondroprotection. Furthermore, interventions for matrix-protection and –remodeling, e.g. with MMP/Aggrecanase-inhibitors (*39*), were recommended. All these approaches were tested in-vitro only so far or in animal experiments, but not in clinical trials, unlike the IA application of anabolic cytokines BMP-7 and FGF-18 : a phase 1 safety study has been performed for BMP-7 (*34*), and a randomized, controlled trial for FGF-18 showing beneficial effects in knee OA patients (*53*). It remains unknown whether anti-inflammatory therapy alone or in combination with the other approaches suffices to protect cartilage following acute injury in order to prevent PTOA.

Issue of application time point

The main theoretical advantage regarding the treatment and prevention of PTOA compared to other forms of OA is that we know the starting time point. This makes early intervention possible, inhibiting the cascades leading to cartilage destruction from the very beginning. Although these considerations reveal the importance of the timing of interventional measures, only 3 studies to date specify the time frame for the treatment applied. The two studies reporting minimal periods of 20 days (*56*) or 3 months (*67*) between trauma and treatment rather addressed treatment options in the post-acute phase. Considering early intervention as a benefit, the intra-articular administration of HA in ankle fractures (*79*) and Anakinra® following ACL tears were applied within the first two weeks after trauma (*48*). In the only ongoing trial using glucocorticoids in patients with ACL rupture, the significance of timing was acknowledged, and study enrollment is mandated within the first week following trauma (*51*).

Which outcome parameter should be applied when evaluating interventional effects in PTOA prevention ?

In clinical trials, outcome parameters are a key issue of relevance and comparability when addressing PTOA prevention. For our patients it is the transfer of knowledge from OA research, pain, disability, and joint instability (*78*) that are the most significant factors. Pain is both extremely relevant and highly suitable for evaluating short-term outcomes. Furthermore, a lot of inflammatory mediators are involved in mediating pain perception. In line with these facts, all the studies identified in this review assessed pain sensation to monitor the success of the intervention applied, 7 studies directly by a visual analog scale, one by a subjective comfort scale and another within established scores. Thus pain assessment should be an essential outcome parameter in PTOA studies. Further criteria

should include quality of life, perhaps evaluated by the EQ5D (*20*), swelling compared to healthy side (delta), joint-specific scores such as the American Orthopedic Foot and Ankle Society score (AOFAS) (*55*) or the Knee Injury and Osteoarthritis Outcome Scores (KOOS) (*67*), gait analysis (*13*), effusion (ultrasound) (*62*), muscle (quadriceps) strength (*16*), and radiological parameters for Magnetic Resonance Imaging (MRI) such as the Knee- (*47*) or the Ankle Osteoarthritis Scoring System (*72*), and the Kellgren Lawrence Score (*42*) for conventional X-rays. Success in treating short-term symptoms associated with OA development should lead the way when evaluating long-term results. This should consider that relevant data on preventing PTOA is not usually obtainable before 10 to 20 years (*54*). These patient-related data should be supported by surrogate parameters such as biomarkers. For example, aggrecan, an essential part of the extracellular matrix, is known to be a reliable and sensitive indicator of OA development in the knee and ankle (*50,72*). Detection and grading of OA is further facilitated by radiographic examinations in association with scoring, which has been previously described for conventional X-rays (*42*) and MRI (*72*) for different joints. MRI is more sensitive as shown in the Framingham OA study, in which pre-radiographic osteoarthritic changes were highly prevalent in the medial patella and medial posterior femur in older persons (*28*). Therefore, challenges in the trial design aiming for a sufficient analysis or influence on PTOA include not only parameters of outcome measurement but also of adequate detection based on clinical and radiographic scores or biomarkers.

CONCLUSION

Although the initial data especially on IA HA injection are encouraging, study designs differ substantially. Therefore, the current data does not allow us to conclude that anti-inflammatory therapy following acute injuries has beneficial effects on short- or long-term outcomes.

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