Review

Most recent developments in strategies to reduce the progression of structural changes in osteoarthritis: today and tomorrow

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Abstract

Osteoarthritis (OA), the most common of all arthritic conditions, is a social and financial burden to all nations. The most recent research has significantly advanced our understanding of the cause of OA and risk factors associated with it. These findings have provided useful information that has helped in the daily management of patients with OA. Some preventative measures and a number of therapeutic agents and drugs are available, which may help to reduce the progression of OA in certain patients. Moreover, the most recent progress in research has significantly enhanced our knowledge of the factors involved in the development of the disease and of the mechanisms responsible for its progression. This has allowed identification of several new therapeutic targets in a number of pathophysiological pathways. Consequently, the field is opening up to a new era in which drugs and agents that can specifically block important mechanisms responsible for the structural changes that occur in OA can be brought into development and eventually into clinical trials.

Introduction

Osteoarthritis (OA) is the most common of the musculoskeletal diseases. Within the context of the ageing population, it is rapidly becoming a significant medical and financial burden to the world. Knowledge of its clinical manifestations and effect on quality of life has helped the medical community to appreciate the real impact of the disease on the health of a steadily increasing number of patients. In response to the need for better medical treatments for OA, several therapeutic strategies have been developed. It is expected that new therapies currently in development will prevent the progression of this debilitating disease. Although significant progress has recently been made in the treatment of a number of arthritic diseases, including rheumatoid arthritis (RA), many difficulties encountered in OA research have hindered the development of effective treatments. The disease develops and changes slowly, and clinically represents a heterogeneous group of disorders that are often referred to as osteoarthritic diseases. The absence of objective and definitive biochemical markers has also been a major hurdle for clinical and therapeutic research.

The development of disease-modifying osteoarthritis drugs (DMOADs) is a rather complex process. A number of obstacles remain including regulatory issues, length of clinical trials, the lack of validation and consensus on new biological markers, and the fact that recent developments in more effective imaging technology are not yet commonly used. Moreover, the duration of treatment is likely to be life long. Most of the DMOADs that have been brought into development thus far have failed because of their safety profile or lack of efficacy. In this regard, one might wonder whether some negative findings of trials might be accounted for by the lack of suitable technology to assess and quantify disease progression reliably. Fortunately, studies completed and underway are providing information that may soon allow us to overcome these hurdles.

A large body of new information has been generated in the past few decades that provides guidance in the development of new and novel therapeutic strategies to delay the progression of structural changes in OA. A comprehensive therapeutic intervention in OA should integrate a clear understanding of the major pathophysiological factors that contribute to the progression of the disease at both clinical and molecular levels. This review focuses on the most recent novel findings in clinical and molecular approaches to improving treatment of OA. The first section reviews the most

ACL = anterior cruciate ligament; ADAMTS = a disintegrin and MMP domain with thrombospondin motifs; BMI = body mass index; CI = confidence interval; COX = cyclooxygenase; CS = chondroitin sulphate; DMOAD = disease-modifying osteoarthritis drug; IL = interleukin; IL-1Ra = IL-1 receptor antagonist; IL-1RacP = IL-1 receptor accessory protein; JSN = joint space narrowing; JSW = joint space width; MMP = matrix metalloprotease; MRI = magnetic resonance imaging; NO = nitric oxide; OA = osteoarthritis; PG = prostaglandin; PPAR = peroxisome proliferator-activated receptor; RA = rheumatoid arthritis; RANK = receptor activator of nuclear factor-κB; sIL-1R = soluble form of IL-1 receptor.

recent findings from clinical studies to guide the management of OA patients, and the second section examines the most promising major pathophysiological targets that have been identified for the development of new DMOADs.

Clinical aspects

For some time the management of clinical OA has largely relied on symptomatic interventions. Recently, however, it has become clear that the management of risks and predisposing factors could yield significant rewards in the fight against OA. New insights gained from a number of clinical studies have enhanced our understanding of the factors associated with disease development and progression. In recent years studies have demonstrated that DMOADs can delay or prevent the evolution of the disease in patients with hip or knee OA. These therapeutic strategies clearly have the advantage that they are readily available and can therefore provide immediate benefits to patients. Moreover, a comprehensive approach combining preventative and curative interventions could provide cumulative benefit.

The following describes what can be done to help reduce the risk for development of disease and its progression, from a practical angle and with the potential for immediate clinical application. A summary of interventions is provided in Table 1.

Table 1

Interventions that potentially reduce progression of structural changes in osteoarthritis

Nonpharmacological and preventative strategies	Pharmaceutical therapies
Weight loss	Inhibition of MMPs, IL-1β
Physical activity	Bone antiresorptive agents
Partial meniscectomy	Neutraceuticals: glucosamine sulphate, chondroitin sulphate
Valgus osteotomy(?)	Intra-articular interventions: steroids, viscosupplementation

IL, interleukin; MMP, matrix metalloproteinase.

Nonpharmacological and preventative strategies

Weight loss and knee structure protection

It is well known that persons who are overweight are at high risk for developing OA of the knee as well as hips and hands. The mechanism by which excess weight causes OA is still poorly understood; a combination of increased force across the joint with systemic/metabolic factors is probably responsible. Although better evidence of the benefit of weight loss is needed, preliminary studies suggest that it can prevent or halt joint damage. A number of studies recently published that examined these phenomena and their impact on OA are of particular interest.

Knee misalignment, obesity and osteotomy

Misalignment of the limbs associated with longstanding obesity is typical in OA and may be a predisposing factor for rapidly progressing knee OA. Felson and colleagues [1] studied veterans and community recruits with symptomatic knee OA. Baseline X-ray films were obtained to assess alignment and disease progression over a 30-month follow-up period. Limb alignment was found to be strongly associated with risk for progression, which was aggravated by an increase in weight (for each 2 kg/m^2 increase in body mass index [BMI]: odds ratio for progression = 1.08, 95% confidence interval [CI] = 1.00–1.16). The effect of BMI on progression was limited to knees with moderate misalignment (odds ratio per 2 kg/m^2 increase in BMI = 1.23, 95% CI = 1.05–1.450), presumably because of the combined focus of load from misalignment and the excess load from increased weight.

In general, knees affected by OA have increased femoral varus. In osteotomy the tibia is usually chosen for varus correction to unload the medial compartment. However, the functional outcome and survival may be limited, and other options have been used with benefit, including femoral and selective double osteotomy. These choices were based on the principle of lessening compartmental overload medially, by correcting the most deformed bone(s) identified by analysis of bone and joint loading contributions.

Sharma and colleagues [2] assessed varus-valgus and anteroposterior laxity in young control individuals, older control individuals without clinical or radiographic OA or a history of knee injury, and patients with knee OA as determined by the presence of definite osteophytes. Their finding of a greater varus-valgus laxity in the uninvolved knees of OA patients compared with older control knees, and an age-related increase in varus-valgus laxity, supports the concept that some portion of the increased laxity of OA may predate disease. Loss of cartilage/bone height is associated with greater varus-valgus laxity. These results raise the possibility that varus-valgus laxity can increase the risk for knee OA and cyclically contribute to disease progression.

Sharma and colleagues [3] further explored this concept in a study involving patients with primary knee OA. Varus alignment at baseline was associated with a fourfold increase in the odds of progression of medial joint space narrowing (JSN), adjusting for age, sex and BMI. Valgus alignment at baseline was also associated with a nearly fivefold increase in the odds of lateral progression; the severity of varus correlated with medial joint space loss ($r = 0.52$, 95% CI = 0.40–0.62 in dominant knees), and the severity of valgus correlated with subsequent lateral joint space loss ($r = 0.35$, 95% CI = 0.21–0.47 in dominant knees).

Therefore, from the above findings, knee misalignment appears to be a clear risk factor for progression of knee OA. Even though it appears logical that correction of misalignment can prevent further knee OA damage, this is not yet proved.

Leptin: a metabolic factor for obesity

Recently, our group commented on the role of leptin as a contributing factor in promoting cartilage damage in OA [4]. Briefly, leptin is the product of the obese (*ob*) gene, and it functions as an afferent signal to influence energy homeostasis through effects on energy intake and expenditure. In joints, leptin levels were recently found to be higher than normal in both human OA cartilage and subchondral bone [5]. In addition, Dumond and colleagues [6] demonstrated that leptin injections in the joints of normal rats can mimic the features of OA. Leptin was also found to be associated with inflammatory states and to stimulate prostaglandin (PG)E_2 and leukotriene production.

Miller and colleagues [7] studied the role of serum leptin and obesity in knee OA patients. The patients were older than 60 years with BMI 28.0 kg/m^2 or greater, had symptomatic knee OA and self-reported difficulty in performing selected physical activities. Participants were randomly assigned to one of four groups for the duration of this 18-month study: healthy lifestyle control; dietary weight loss; exercise training; and a combination of dietary weight loss and exercise training. The diet and diet plus exercise groups lost 5.3% and 6.1% of their weight, respectively; the exercise group lost 2.9%. Weight loss resulted in a significant decrease in the level of serum leptin at the 6-month and 18-month time points for the diet and diet plus exercise groups as compared with the other two groups ($\beta = 0.245$; $P < 0.01$). These findings could imply that a decrease in serum leptin may be one mechanism by which weight loss slows progression of disease in patients with OA.

Altogether, these findings suggest a possible link between abnormal lipid metabolism and connective tissue in OA. However, this does not preclude the involvement of other local factors. Hence, leptin might be a contributing factor that alone may be insufficient yet necessary to promote cartilage damage in OA.

With the information gained from these recent studies, and while factoring in joint alignment and metabolic mediators such as leptin, it is still appropriate to promote weight loss to our patients as an excellent way to alleviate pain and potentially prevent further knee joint damage induced by OA.

Physical activity and the role of muscle strengthening in preventing osteoarthritis

Exercise is an effective intervention in OA and is an important component in its prevention. Well conditioned muscle and muscular balance are needed to attenuate impact loads, provide joint stability, and support function and independence. Clinical trials have provided strong evidence of the efficacy of muscle conditioning in lessening symptoms in patients with knee OA [8-10].

Some time ago Lane and colleagues [11] demonstrated the longitudinal effects over 5 years of running and ageing on the development of radiographic and clinical OA of the knees, hands and lumbar spine. Running did not accelerate the development of radiographic or clinical OA of the knee, whereas 12% of all participants developed knee OA with ageing. Lane and colleagues [12] revisited that cohort 4 years later to look at the associations between running and radiographic hip OA and the progression of radiographic knee OA. They compared members of the running club (age 60–77 years) and nonrunner control individuals using clinical examination, annual questionnaires and X-ray films taken of the knees and hips. The presence of radiographic hip OA and the progression of radiographic knee OA remained similar for older runners compared with nonrunners.

A recent study [13] even demonstrated positive effects of moderate exercise on glycosaminoglycan content in knee cartilage. This 4-month trial conducted in 45 individuals demonstrated that a supervised, moderate, thrice weekly exercise program yielded an improvement in knee cartilage glycosaminoglycan content, as assessed by magnetic resonance imaging (MRI), compared with no intervention. However, the precise implications of these findings for changes in OA cartilage over time remain to be established in future long-term studies.

Menisci and anterior cruciate ligament lesions

Unfortunately, knee injuries also occur commonly in sports, limiting field and practice time and performance level. The Clearwater Osteoarthritis Study [14] recently evaluated the association between acute knee injury and OA. Among the 1436 men and women aged 40 years and older participating in the population-based study, individuals with a history of knee injury were 7.4 times more likely to develop knee OA than were those with no history of knee injury.

Anterior cruciate ligament injury and knee osteoarthritis

The aetiology of injury relates primarily to sports-specific activity, and female athletes are at greater risk for knee injury than are their male counterparts in many sports. Particular pain syndromes such as anterior knee pain and injuries such as noncontact anterior cruciate ligament (ACL) injuries occur at a higher rate among female athletes than in male athletes at a similar level of competition. Beyond real-time pain and functional limitations, previous injury is implicated in knee OA occurring later in life.

Lohmander and colleagues [15] found a higher prevalence of knee OA, pain and functional limitations in female soccer players 12 years after ACL injury. Eighty-four injured female soccer players underwent knee radiography. The mean age at assessment was 31 years (range 26–40 years) and the mean BMI was 23 kg/m^2 (range 18–40 kg/m^2). Fifty-five women had radiographic changes in their index knee, and 34 fulfilled the criteria for radiographic knee OA. Slightly more than 60% of the players had undergone reconstructive surgery of the ACL. Using multivariate analyses, surgical reconstruction was found to have no significant influence on knee symptoms.

Using MRI, Hill and colleagues [16] evaluated the prevalence of ACL rupture in knees with symptomatic OA as compared with the prevalence in those without OA, and the relationship to pain and recalled injury. MRI and plain X-ray films of the knee were performed in a group of patients with painful knee OA and individuals without knee pain. The proportion of cases with complete ACL rupture was 22.8% as compared with 2.7% among control individuals ($P = 0.0004$). Cases with ACL rupture had more severe radiographic OA ($P < 0.0001$) and were more likely to have medial JSN ($P < 0.0001$); however, they did not have higher pain scores. ACL rupture is more common among those with symptomatic knee OA than in those without knee OA. Fewer than half of individuals with ACL rupture recall a knee injury, suggesting that this risk factor for knee OA is largely underestimated.

In summary, acute knee injury, and especially ACL damage, is clearly associated with the occurrence of OA and its progression. Unfortunately, this pathology is often unrecognized, and even if the ACL is repaired the development and progression of OA might not be prevented.

Meniscal lesions and osteoarthritis: chicken or egg?

Isolated meniscal tear and subsequent repair, or partial or total rupture of the ACL without major concomitant injuries appear to increase the risk for knee OA by 10-fold (15–20% incidence) compared with an age-matched, uninjured population (1–2%). Meniscectomy in a joint with intact ligaments further doubles the risk for OA (30–40%), and 50–70% of patients with complete ACL rupture and associated injuries have radiographic changes after 15–20 years. Thus, an ACL rupture combined with meniscus tear or other knee ligament injury results in knee OA in most patients. About 10–20 years after ACL injury, OA often presents as a slight joint space reduction or, occasionally, as joint space obliteration, but it is usually not associated with major clinical symptoms. According to the few longitudinal studies performed, the progression of OA changes is slow, and in many cases the problems requiring treatment may be encountered only 30 years or more after the initial accident.

Meniscal structural damage as a manifestation of knee osteoarthritis

Meniscal damage has been suggested to be an important part of the overall pathophysiology of knee OA. However, whether meniscal damage or cartilage degradation occurs first is still unknown. Animal model data suggest that meniscal damage may occur at the early stages of the disease while cartilage damage appears later [17]; however, others have suggested otherwise [18]. Interestingly, a recent study [19] reported that, in a cohort of 32 primary OA patients, 75% had mild-to-moderate or severe meniscal damage (tear or extrusion). That study further showed a highly significant loss of cartilage volume, quantified using MRI, in severe medial meniscal tear compared with absence of tear ($P = 0.002$). An even greater loss of cartilage volume in the medial compartment of the knee was observed when the medial meniscal tear ($P < 0.0001$) and extrusion ($P < 0.001$) were present, reflecting more rapid disease progression in this area. These findings were confirmed in another large population-based study [20].

Meniscal repair: conservative versus radical meniscectomy

Englund and colleagues [21] looked at patients with intact cruciate ligaments who had undergone meniscectomy an average of 16 years earlier and compared them with control individuals. The authors concluded that an isolated meniscal tear treated by limited meniscectomy is associated with a high risk for radiographic and symptomatic tibiofemoral OA at 16 years of follow up. However, the outcome was worse with extensive resections of the meniscus.

Another study conducted by the same authors [22] examined the risk factors for symptomatic knee OA 15–22 years after meniscectomy, at which time they investigated the influence of age, sex, BMI, extent of meniscal resection, cartilage status, and knee load on the development of radiologically evident OA of the knee and joint symptoms after meniscal resection. Obesity, female sex and pre-existing early-stage OA were features associated with poor self-reported and radiographic outcome. Controlling for all of these risk factors for disease progression, partial meniscal resection was associated with less radiographic OA over time than total meniscectomy, clearly suggesting that a more conservative approach should be taken while performing such surgery.

Thus, meniscal tear and extrusion are risk factors strongly associated with the development and progression of knee OA.

In summary, low-grade repetitive impact such as running does not seem to be associated with the occurrence and worsening of knee OA. Early diagnosis and effective treatment of joint injuries and ensuring complete rehabilitation after joint injury should decrease the risk for OA among sports participants. When performing surgical repair, the intact meniscal tissue should be untouched in order to confer optimal knee stability and protection.

Subchondral bone oedema and bone resorption

Recent studies clearly demonstrated the role of subchondral bone in the pathophysiology of OA [23,24]. With refinements in MRI knee acquisition, researchers are now able to identify markers and predictors of disease progression. Felson and colleagues [25] recently demonstrated that, in patients with knee OA, bone marrow lesions were found in greater number and larger size in patients with pain than in those with no pain ($P < 0.001$), even after adjustment for severity of radiographic disease, knee effusion, age and sex. Moreover, the same research team demonstrated that the presence of bone marrow oedema is related to progression of knee OA [26]. The presence of bone resorption is also strongly recognized as part of OA progression. Recent work conducted by

Bettica and colleagues [27] demonstrated that general bone resorption (indicated by type I collagen amino-terminal and carboxyl-terminal telopeptide biomarker measurements) is increased in patients with progressive knee OA, as defined by 4-year radiological progression. This increased bone resorption was similar to that observed in patients with osteoporosis. The same group demonstrated [28] that this finding was independent of bone formation, calcium, or vitamin D regulation. Messent and colleagues [29] used fractal signature analysis to assess specific tibial cancellous subchondral bone changes in patients with knee OA. In that 24-month longitudinal study the investigators showed that bone loss occurred in all patients with OA in the medial compartment. A decrease in 'fractal dimension' of vertical and horizontal trabeculae, consistent with a decrease in trabecular number, was correlated with detectable knee JSN.

These exciting results shed new light on the implications of bone changes for the aetiology of OA and may provide new strategic therapeutic targets.

Pharmacological therapies

As indicated above, the pathophysiological events associated with OA are becoming increasingly understood. Recent observations suggest that therapy can now be targeted at specific pathophysiological pathways. Thus far a number of agents and drugs have demonstrated activity in reducing the progression of structural changes in certain tissues of the OA joint.

Inhibition of cartilage degradation

Matrix metalloprotease inhibitors

For several decades it has been recognized that matrix metalloproteases (MMPs) play a role in the pathologic breakdown of the joint extracellular matrix in OA. This understanding has stimulated a search for a number of synthetic MMP inhibitors that could serve as potential therapeutic agents.

It is now appreciated that tetracycline analogues can inhibit MMPs, and multiple underlying mechanisms have been proposed. Tetracycline analogues are currently on the threshold of approval as anti-MMP agents for the treatment of periodontitis, which is another extracellular matrix destructive disease, and this indication could eventually be extended to OA and RA. In this regard, specially formulated low-dose regimens of a commercially available tetracycline analogue, namely doxycycline, have been used in long-term clinical trials and were found to reduce extracellular matrix breakdown, including bone loss, in adult periodontitis.

Brandt and colleagues [30] recently examined the effects of doxycycline on OA progression in a randomized, placebo-controlled, double-blind trial. The primary outcome measure was JSN in the medial tibiofemoral compartment. Obese women aged 45–64 years with unilateral radiographic knee OA were randomly assigned to receive 30 months of treatment with 100 mg doxycycline or placebo twice a day. Tibiofemoral JSN was measured by standardized radiographic examinations. After 16 months of treatment, the mean (± standard deviation) loss of joint space width (JSW) in the index knee in the doxycycline group was 40% less than in the placebo group (0.15 ± 0.42 mm versus 0.24 ± 0.54 mm); after 30 months it was 33% less (0.30 ± 0.60 mm versus 0.45 ± 0.70 mm). However, doxycycline did not reduce the mean severity of joint pain. In contrast, doxycycline had no effect on either JSN or pain in the contralateral knee. This study showed that doxycycline can reduce the rate of JSN in established OA. Its lack of effect on the contralateral knee, in which the disease is less severe, suggests that pathogenic mechanisms in that joint were perhaps different from those in the index knee.

This study provides the first proof of concept of the effectiveness of anti-MMP strategies for developing DMOADs. Inhibition of the MMP superfamily is a very logical objective in OA. However, only doxycycline has thus far made it to the final stages of a trial. The reasons why the symptoms were not alleviated in this unique trial are intriguing. Further studies are needed before we may consider tetracycline or its analogues to be an effective treatment that can prevent knee OA progression.

Cytokine inhibition

Recent evidence has implicated a number of cytokines, particularly IL-1, in the OA process of cartilage destruction. IL-1β is probably the principal cytokine responsible for the signs and symptoms of inflammation present in patients with OA. Data show that the action of this cytokine can also be reduced by several means within the clinical context of OA.

One compound is rhein, the active metabolite of diacerein, which inhibits IL-1 synthesis and activity. Data from OA animal models showed that diacerein reduced articular cartilage damage. In clinical trials oral diacerein was associated with significant improvement in the symptoms of patients with hip and/or knee OA.

Pelletier and colleagues [31] demonstrated that the optimal daily dose of diacerein for symptomatic relief of patients with knee OA was 100 mg (50 mg twice daily). Dougados and colleagues [32] evaluated the structure-modifying effects of diacerein in 507 patients with primary hip OA in a randomized, double-blind, placebo-controlled, 3-year study. Patients received diacerein (50 mg twice daily) or placebo. The minimal hip JSW was measured yearly on pelvic X-ray films. The percentage of patients with radiographic progression (joint space loss ≥0.5 mm) was significantly lower in patients receiving diacerein than in patients receiving placebo. Diacerein, however, had no evident effect on the symptoms of OA in this study.

Selectively targeting IL-1 is probably among the most promising OA treatment strategies. Long-term efficacy and

safety data are now available on the oral preparation diacerein, which has been used for many years in Europe. However, there remains a need for additional pivotal studies on diacerein, particularly on knee OA structure.

The use of intra-articular approaches may also be considered. Indeed, intra-articular injection of IL-1 receptor antagonist (IL-1Ra) in patients with symptomatic knee OA was recently assessed [33]. An open prospective multicentre trial was conducted using six doses of IL-1Ra, from 0.05 mg up to 150 mg. The trial was double-blind with respect to the dose administered. Significant improvements on knee OA symptoms were still observed at 3 months in the patients who received 150 mg IL-1Ra. The results of this pilot study, however, could not be confirmed in another recent phase II double-blind study [34].

Nutraceuticals: glucosamine sulphate and chondroitin sulphate

Glucosamine has been evaluated for its efficacy in relieving the symptoms of OA and for its disease-modifying potential. Reginster and colleagues [35] reported a landmark randomized clinical trial on the long-term effects of glucosamine sulphate on OA progression. Patients with knee OA were randomly assigned to 1500 mg oral glucosamine sulphate or placebo once daily for 3 years. X-ray films of weight-bearing knees were taken at enrolment and after 1 and 3 years, and minimum JSW was measured by visual inspection. Symptoms were scored using the Western Ontario and McMaster Universities index. The patients on placebo had progressive JSN, with a mean joint space loss after 3 years of −0.31 mm (95% CI = −0.48 mm to −0.13 mm), whereas there was no significant joint space loss in the patients on glucosamine sulphate (−0.06 mm, 95% CI = −0.22 mm to +0.09 mm). Knee OA symptoms worsened slightly in the patients on placebo compared with the improvement observed after treatment with glucosamine sulphate. The long-term combined structure-modifying and symptom-modifying effects of glucosamine sulphate suggest that it could be used as a disease-modifying agent in OA. These findings were also corroborated by two studies conducted by Pavelka [36] and Bruyere [37] and their groups using similar trial designs.

Chondroitin sulphate (CS) exhibits a wide range of biological activities, and from a pharmacological point of view it is believed to produce a slow but gradual decrease in the clinical symptoms of OA that could last for a long period of time after treatment. In theory, CS could also act as an anti-inflammatory and chondroprotective agent by modifying the structure of cartilage.

Two recently published studies looked specifically at CS in patients with knee OA. A randomized controlled trial conducted by Michel and colleagues [38] examined the effects of chondroitin-4 and chondroitin-6 sulphate in knee OA patients, who were randomly assigned to receive either 800 mg CS or placebo once daily for 2 years. The primary outcome was joint space loss over 2 years, as assessed by a posteroanterior X-ray film of the knee in flexion; secondary outcomes included pain reduction and improved function. The patients receiving placebo had progressive JSN, with a mean (± standard deviation) joint space loss of 0.14 ± 0.61 mm after 2 years ($P = 0.001$) as compared with baseline, whereas there was no change for those receiving CS (0.00 ± 0.53 mm). However, no significant symptomatic effect was found. These findings were recently corroborated in a study conducted by Uebelhart and colleagues [39], who looked at the effect of intermittent treatment of knee OA with oral CS in a 1-year clinical trial. Radiographic progression at 12 months revealed a significant decrease in JSW in the placebo group with no change in the CS group, providing additional evidence of the structure-modifying properties of CS in knee OA.

The preliminary results of a recent study sponsored by the US National Institutes of Health examining the symptomatic effects of glucosamine-HCl and CS alone or in combination recently became available [40]. The results indicate that combined treatment with CS and glucosamine-HCl was effective at relieving OA symptoms, but this was the case only in those patients with moderate to severe baseline knee pain.

Use of glucosamine-HCl and CS is extremely popular worldwide. It is safe but requires chronic use. The aforementioned studies of treatment efficacy are intriguing but have some limitations, which could dampen the enthusiasm for this form of treatment. An important study on the structural protective effects in knee OA sponsored by the US National Institutes of Health is nearing completion and should provide further enlightenment on the disease-modifying potential of these agents in OA.

Intra-articular treatments: steroids and hyaluronic acid

The pain and secondary inflammation in OA can be effectively relieved by intra-articular injection of steroids. However, the long-term impact and safety of such injections, especially on knee anatomical structure, were unknown until recently.

Raynauld and colleagues [41] looked at the safety and efficacy of long-term intra-articular steroid injections in OA of the knee in a randomized, double-blind, placebo-controlled setting. The patients received intra-articular injections of triamcinolone acetonide 40 mg (34 patients) or saline (34 patients) in the study knee every 3 months for up to 2 years. The primary outcome variable was radiographic progression of JSN of the injected knee after 2 years. The clinical efficacy measure of primary interest was the pain subscale from the Western Ontario and McMaster Universities index. At the 1-year and 2-year follow-up evaluations, no difference was noted between the two treatment groups with respect to loss of joint space over time. However, the steroid injected knees exhibited a trend toward greater symptom improvement. Although no disease-modifying activity of steroid injections

was demonstrated, these findings support the long-term safety of intra-articular steroid injections in patients with symptomatic knee OA.

Joint lubrication is naturally provided, at least in part, by hyaluronic acid in the synovial fluid. Hyaluronan is present in abundance in normal young and healthy joints. In degenerative OA, hyaluronan is smaller in size and molecular weight, and its concentration is diminished. It is believed that this decrease in joint lubrication and reduction in the shock absorbing mechanism in OA can be remedied by intra-articular viscosupplementation. This approach has been used for many years but the actual impact on knee structure was not studied until recently.

Jubb and colleagues [42] conducted a 1-year, randomized, placebo (saline)-controlled clinical trial of 500–730 kDa sodium hyaluronate on radiographic changes in OA of the knee. A total of 319 individuals completed the 1-year study (hyaluronic acid, 160 patients; placebo, 159 patients). Although no significant differences were found between hyaluronic acid and saline treatment groups on knee OA radiographic progression, those with milder disease at baseline (defined radiographically) had lesser progression of JSN with hyaluronic acid treatment.

A local disease such as knee OA may mandate a local therapy such as intra-articular injections. Only one study has looked at the long-term impact of repetitive intra-articular steroid injections and, although it was underpowered, this study [41] suggested that the approach is safe with respect to knee structure and is effective in relieving symptoms. Hyaluronic acid and hyaluronic acid derivative injections are also effective for selected OA patients and are safe. The rare occurrence of an acute local reaction is easily managed. However, more data on the effect of viscosupplementation on structure is needed in order to evaluate whether it can truly prevent progression of knee OA.

Inhibition of subchondral bone remodelling

Antiresorptive agents

As mentioned above, recent research has highlighted the importance of subchondral bone as a target for therapeutic intervention and disease modification in OA [23,24]. Joints affected by OA exhibit increased bone turnover, which consequently increases the possibility of benefiting from drugs that alter bone metabolism, particularly the antiresorptive agents such as bisphosphonates. A number of clinical studies have tested the efficacy and safety of bisphosphonates in order to explore their potential in the treatment of OA, and two studies examining the effectiveness of antiresorptive agents in postmenopausal women with knee OA were recently published.

Carbone and colleagues [43] conducted a study to examine the association between use of medications that have a bone antiresorptive effect (oestrogen, raloxifene and alendronate) on the structural features of knee OA, evaluated using MRI and radiography. The women treated with both alendronate and oestrogen exhibited significantly less knee subchondral bone attrition and bone marrow oedema-like abnormalities, as assessed by MRI, than did those who had not received these medications. No significant effect on progression of cartilage damage was identified.

On the other hand, Spector and colleagues [44] examined the effect of risedronate, a bisphosphonate, on joint structure and symptoms of patients with primary knee OA. In a 1-year prospective, double-blind, placebo-controlled study, 284 patients (aged 40–80 years) with mild-to-moderate OA of the medial compartment of the knee were enrolled. Patients were randomly assigned to once-daily risedronate (5 mg or 15 mg) or placebo. X-ray films were taken at baseline and 1 year to assess JSW. A definite trend toward improvement was observed in a phase II study in both joint structure and symptoms in patients with primary knee OA treated with risedronate. However, the study was underpowered to detect joint protection with this bisphosphonate clearly. The results of the study could not be confirmed in a phase III study, although a clear antiresorptive effect of risedronate could be found at the subchondral bone level.

The use of a bisphosphonate to treat knee OA and prevent its structural progression needs to be explored further. There is a good rationale to use such agents because they are safe for long-term administration (data from the osteoporosis studies) and easy to administer. However, some results from a major phase III trial were disappointing. Because selection of patients with lengthy disease duration on study entry is a potential explanation for the results, further trials, perhaps in patients with less advanced disease and using more reliable and sensitive imaging technologies such as MRI, are needed before use of bisphosphonates to treat OA may be considered.

The most attractive therapeutic targets: expectations for the future

There is still much to be accomplished in the field of OA, particularly with respect to the discovery of new strategies and treatments that can effectively stop the progression of the disease. Nevertheless, recent advances in OA research have identified several pathways that are believed to play predominant roles in the evolution of the disease process and structural changes. What major advances in therapeutic targets can we foresee for the future of OA? The following section reviews a number of strategies, summarized in Table 2, that are believed to involve the most logical and promising targets for the development of DMOAD therapies.

Targeting synovial inflammation

Among the significant structural changes that take place during the development of OA is the presence of synovial inflammation. The synthesis and release of a number of

Table 2

The most attractive therapeutic targets for the development of disease-modifying osteoarthritis drugs

Target	Examples (where applicable)
Inflammatory process	Cytokines (IL-1β) Nitric oxide and reactive oxygen species Eicosanoids: leukotrienes and prostaglandins together
Ligand to PPARγ	
Cartilage degradation	MMP-13 Aggrecanase-2 (ADAMTS-5)
Subchondral bone remodelling factors	

ADAMTS, a disintegrin and MMP domain with thrombospondin motifs; IL, interleukin; MMP, matrix metalloprotease; PPAR, peroxisome proliferator-activated receptor.

mediators by the inflamed tissue is an important factor in the development and/or progression of OA changes. As previously mentioned, among the inflammatory factors the proinflammatory cytokine IL-1β plays a central role in OA pathophysiology. Factors that regulate its synthesis and/or activity are therefore favoured targets. Other approaches are broader and include activating or increasing the level of factors able to inhibit proinflammatory cytokines or other catabolic factors.

Interleukin-1β

For specific inhibition of the production/activity of IL-1β, basic research has demonstrated that various strategies can be used. These include receptor blockade, neutralization of the cytokine by soluble receptors or monoclonal antibody, blocking the formation of active IL-1β, or inhibiting the IL-1β cellular signalling pathways. One strategy (as mentioned above under Cytokine inhibition and below under Gene therapy) is the use of recombinant human IL-1Ra. This factor is a competitive antagonist of IL-1 that blocks the actions of IL-1 without any detectable agonist activity. Reports indicate that Anakinra (a recombinant methionyl human IL-1Ra; Amgen, Thousand Oaks, CA, USA), when injected subcutaneously, is safe and well tolerated in a diverse population of patients with RA, and slows radiographically observed progression of the disease [45]. However, its rapid clearance as well as the difficulty of knowing how much of the injected material accumulates in the OA joints has thus far promoted the strategy of delivering IL-1Ra intra-articularly (see Pharmacological therapies, above).

Soluble receptors play an important physiological role in neutralizing cytokines. The transmembrane domain of both IL-1 receptors (IL-1 receptor I and IL-1 receptor II) is susceptible to lysis by proteases, leading to the release of a soluble form of the receptor (sIL-1R). Free IL-1 binds to its specific sIL-1R, resulting in less IL-1 being available to bind to the membrane-specific receptor. However, IL-1Ra also binds the sIL-1R, and the binding affinity of sIL1R to both IL-1 isoforms and IL-1Ra differs. Type II sIL-1R binds IL-1β more readily than IL-1Ra; in contrast, type I sIL-1R binds IL-1Ra with high affinity [46-48]. Therefore, the strategy using type II sIL-1R alone or in combination with IL-1Ra would seem more promising. However, soluble receptors have short plasma half-lives, and repeated doses would be required to neutralize the effects of the cytokine. This limitation can be circumvented by conjugating soluble receptors with a human proteolytic fragment of IgG, which can extend the half-lives of these molecules. Another alternative that has been used for the tumour necrosis factor-α is to polymerize the soluble receptor; this can reduce antigenicity and prolong the half-life.

Data on IL-1 signalling show that after IL-1 binding to the cell membrane IL-1 receptor I, the IL-1 receptor accessory protein (IL-1RAcP) is recruited to form a high-affinity receptor complex, which initiates the intracellular signalling cascade [49,50]. In collagen-induced arthritis, treatment with sIL-1RAcP had a marked effect when given prophylactically [51]. The characteristics of this molecule make it an interesting inhibitor of IL-1 activity because it competes with membrane-bound IL-1RAcP for receptor complex formation with IL-1 receptor I. Moreover, sIL-1RAcP is an IL-1-specific target cell discriminating inhibitor, because it can only induce functional inhibition in the presence of IL-1 bound to IL-1 receptor I. sIL-1RAcP can also interact with the type II sIL-1R or shed type II IL-1R, resulting in the formation of soluble IL-1 scavenger receptor. A report indicates that sIL-1RAcP associates as ligand-bound to type II sIL-1R, increasing the binding affinity of IL-1α and IL-1β to type II sIL-1R by approximately 100-fold, while leaving unaltered the low binding affinity of IL-1Ra to type II sIL-1R, thus enhancing inhibition of IL-1 when both IL-1Ra and sIL-1RAcP are present [52].

Relevant to the IL-1 neutralization strategy, Economides and colleagues [53] engineered a high-affinity 'trap' by combining the extracellular domains of both the IL-1 receptor I and IL-1RAcP. This IL-1Trap preferentially binds IL-1β. A phase II clinical trial for the treatment of RA has been initiated [54].

The use of antibodies against IL-1 or against IL-1 receptor I is another approach to neutralizing this cytokine. The type of antibody appears to be critical to its clinical efficacy. The concept is to use chimaeric and humanized monoclonal antibodies, which should be less immunogenic than murine monoclonal antibodies (first utilized for RA). No study has yet been conducted in patients with OA.

IL-1β is primarily synthesized as a precursor (pro-IL-1β), and must be cleaved by a cysteine-dependent protease, named IL-1β converting enzyme (or caspase-1), to generate the mature cytokine. In OA tissues, this enzyme was also found to

be intimately involved in the maturation of IL-1β [55]. It is also responsible for the cleavage and release of mature IL-18. Thus, an inhibitor against this enzyme will block activation of two very potent proinflammatory cytokines. IL-1β converting enzyme inhibitor was found to reduce the progression of joint damage in two experimental mouse models of OA [56]. A recent clinical trial conducted in RA patients was terminated because of what is believed to be toxicity.

IL-1 activity is mediated by its binding only to type I receptor; type II receptor did not mediate IL-1 activity. After IL-1 binding to its type I receptor, there is induction of multiple phosphorylation-dependent signalling pathways that regulate gene expression. These pathways include the serine-threonine kinases of the mitogen-activated protein kinase family and nuclear factor-κB cascades. It is now recognized that the mitogen-activated protein kinase superfamily is composed of at least three main and distinct signalling pathways: the extracellular signal-regulated protein kinases, the c-Jun amino-terminal kinases or stress-activated protein kinases, and the p38 family of kinases.

To date, at least one experimental *in vivo* study has reported a therapeutic effect of a specific extracellular signal-regulated protein kinase inhibitor, namely PD198306, in experimental rabbit OA [57]. It was associated with significant reductions in structural changes (cartilage destruction and osteophyte width) and in the severity of synovial inflammation.

c-Jun amino-terminal kinase inhibitors also have demonstrated preventative effects on the destruction of bone and cartilage in RA [58-60]. However, little is known about the effect of these compounds in OA models. It was recently reported that phenyl N-tert-butylnitrone, a spin-trap agent, downregulates IL-1-induced MMP-13 expression via the inhibition of the c-Jun amino-terminal kinase pathway in OA chondrocytes [61].

The p38 inhibitor SB203580 had anti-inflammatory effects in cartilage explants and in animal models. In bovine cartilage explants, it blocked IL-1-mediated collagen breakdown, whereas proteoglycan degradation was unaffected [62]. However, p38 mitogen-activated protein kinase inhibitors were shown to blunt chondrocyte and cartilage proteoglycan synthesis in response to transforming growth factor-β, but the response to insulin-like growth factor-I was unaffected. In the collagen-induced arthritis model of RA, SB203580 inhibited tumour necrosis factor-α and IL-6 production, reduced paw inflammation, and inhibited the formation of joint lesions [63]. The p38 inhibitors also decreased levels of nitric oxide (NO).

Other inflammatory mediators

Blocking inducible nitric oxide

NO is an interesting target in the context of OA for at least two main reasons. First, NO and its byproducts are able to induce the inflammatory component of OA; NO can increase the activity of cyclo-oxygenase (COX)-2/PGE_2 and consequently appears to be responsible for an increase in the signs and symptoms of the disease. Second, it can also induce tissue damage and destruction. Therefore, it is believed that reducing the levels of inducible NO synthase (the enzyme responsible for augmented production of NO) not only may reduce the symptoms but also is likely to slow disease progression, allowing this approach to tackle two targets simultaneously. This hypothesis is supported by positive findings *in vivo* on the progression of lesions in studies conducted in the experimental canine model of OA [64-66].

Blocking the cyclo-oxygenase and leukotriene pathways

In view of the concept that prostaglandins and leukotrienes have complementary effects in perpetuating the inflammatory process, and that chronic inhibition of COX may lead to a shunt of arachidonic acid metabolism toward the leukotriene pathway, blocking both prostaglandin and leukotriene B_4 production could have synergistic effects and achieve optimal anti-inflammatory activity. A novel dual COX/5-lipoxygenase inhibitor (Licofelone; Merckle GmbH, Ulm, Germany) is now in phase III clinical development. This compound is an arachidonic acid substrate analogue that inhibits both COX and 5-lipoxygenase [67,68]. In animal models, Licofelone exhibits anti-inflammatory, analgesic and antipyretic properties [69]. Data from the experimentally induced OA canine model [70-72] revealed that this compound significantly reduced the severity of cartilage and subchondral bone alterations, as well as several disease pathways.

Peroxisome proliferator-activated receptor gamma

The peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that act as anti-inflammatory agents. To date, three different PPARs have been identified and cloned: PPARα, PPARβ and PPARγ. Among the PPARs, it appears that PPARγ is the key factor involved as an anti-inflammatory agent. It has been found to be expressed in various cells, including human chondrocytes and synovial fibroblasts [73,74]. Moreover, deoxy-$\delta^{12,14}PGJ_2$, a metabolite of COX-2 activity, is a natural ligand of PPARγ and demonstrated anti-inflammatory properties in a PPARγ-dependent or PPARγ-independent manner. *In vitro*, deoxy-$\delta^{12,14}PGJ_2$ inhibits IL-1-induced MMP-13, COX-2, NO production and proteoglycan degradation in chondrocytes, and IL-1-induced microsomal PGE synthase-1 in synoviocytes [73-77]; the latter enzyme is the last key step in the formation of PGE_2. *In vivo*, the synthetic PPARγ ligands rosiglitazone and pioglitazone were capable of improving signs of inflammation and histological lesions in a collagen-induced arthritis model [78] and an OA guinea pig model [79], respectively.

Targeting cartilage destruction

One of the primary causes of cartilage degradation lies in the destruction of matrix induced by elevated levels of a number of proteolytic enzymes. Among these are two main enzyme

families: the MMPs, which can degrade the major components of the extracellular matrix; and the ADAMTS (a disintegrin and MMP domain with thrombospondin motifs) family, which mediates mostly cartilage aggrecan loss.

Metalloproteases

In human OA cartilage, the most prominent MMPs are collagenases, stromelysin and gelatinases. Inhibition of the synthesis/activity of these enzymes as a treatment for OA has been the focus of intensive research for many years. To date, the most promising strategy is the use of chemical molecules that can block the activity of MMPs. The action of MMPs can be controlled in a number of ways, but the main avenues explored are inhibition of their synthesis and transformation of the pro into active MMPs. A number of these compounds has already been tested in clinical trials, and data have shown that MMP inhibitors may produce musculoskeletal side effects characterized by joint stiffness, joint fibroplasias and accumulation of type I collagen in the affected joints [80]. It has been speculated that sheddase inhibition (specific inhibition of tumour necrosis factor-α converting enzyme/ADAM-17) may be responsible for the observed side effects. Drug development efforts are now being directed at the use of selective inhibitors against proteases rather than broad protease inhibition. The main reason for this is based on the hypothesis that such an approach will allow certain side effects to be avoided. However, compounds selective for a single MMP member have been difficult to develop. Moreover, as ADAM family members also manifest the MMP signature sequence, discrimination between these two families has been a further challenge. Recently, MMP-13 was identified as one of the most attractive targets for the treatment of OA, and there are now compounds that are claimed to be MMP-13 selective [81,82].

Doxycycline (a tetracycline analogue) was demonstrated in *in vitro* and *ex vitro* studies to inhibit the synthesis and activity of collagenase and gelatinase, and to reduce disease progression in two animal models of OA when given prophylactically. As mentioned above (under Matrix metalloprotease inhibitors), a recent study demonstrated that oral doxycycline can slow the rate of radiographic progression in knee OA [30].

Aggrecanases

The proteases responsible for the cleavage of aggrecan were designated aggrecanases. Two such enzymes were found in articular tissues and named aggrecanase-1 and aggrecanase-2 [83,84]. These enzymes belong to the ADAMTS family and were further designated ADAMTS-4 and ADAMTS-5, respectively. Recent reports have shown that ADAMTS-5 is the predominant enzyme involved in the OA process [85,86]. Synthetic inhibitors originally targeted for MMPs often inhibit aggrecanase. Although no true selective inhibitor of aggrecanase has been reported, efforts to discover tumour necrosis factor-α converting enzyme/ADAM-17 inhibitors have uncovered a series of compounds with remarkable aggrecanase selectivity [87]. A selective inhibitor of aggrecanase and MMP-13 was recently reported [88].

Targeting subchondral bone remodelling

The ultimate goal in the treatment of OA is to improve or preserve the patient's joint structure by preventing its destruction. It is hypothesized that subchondral bone, rather than cartilage, may be the site of the aetiologically most significant pathophysiological events [23,24]. Therefore, one may believe that therapies that interfere with bone remodelling could block or at least attenuate the progression, not only of tissue changes but also of cartilage alterations. The rationale in a number of studies in preclinical models of OA was based on data showing that subchondral bone changes are mainly resorptive in nature within the time schedule set for the treatment study, and anti-resorptive agents could reduce OA progression.

Treatment with calcitonin [89] of the experimental dog ACL model of OA was found to reduce the level of urinary bone resorption biomarkers (pyridinium crosslinks), the severity of cartilage lesions and the size of osteophytes. Similar findings were reported in the same animal model with the bisphosphonate ethidronate [90,91], and in the rat ACL model [92] with alendronate treatment. The effect of alendronate was linked to its action of reducing local synthesis of active transforming growth factor-β and MMP-9 in bone, as well as MMP-13 in cartilage. These findings are in accordance with a study conducted in the dog ACL model in which Licofelone, a dual inhibitor of 5-lipoxygenase and COX activity, inhibited the development of cartilage lesions and subchondral bone resorption by reducing the synthesis of MMP-13 and cathepsin K, as well as other enzymes and growth factors that are involved in bone remodelling [93]. Altogether, these data strengthen the notion that therapeutic interventions that effectively inhibit bone resorption could potentially be used as DMOADs.

Most recent knowledge on the underlying molecular pathological mechanisms that lead to bone remodelling/resorption in arthritic diseases such as OA will help to bring new therapeutic strategies to clinical practice. For instance three factors, namely receptor activator of nuclear factor-κB (RANK) ligand and osteoprotegerin, were clearly demonstrated to be key elements involved in bone resorption. Excessive production of RANK ligand and/or osteoprotegerin deficiency may therefore contribute to increased bone resorption. Clinical trials are already underway using osteoprotegerin and anti-RANK ligand antibodies to test their efficacy in the treatment of osteoporosis [94] and of bone erosions in RA patients. The potential of these agents as DMOADs is very appealing within the context of the subchondral bone remodelling taking place in OA and its probable role in the pathophysiology of cartilage degradation. Only appropriate clinical trials will be able to provide the information needed to address this important question.

Future prospects

Pharmacogenomics

The rapid development of knowledge in the field of genomics and proteomics has revolutionized the approach to the development of new treatments for diseases. The presence of a single cell population in cartilage has made it easier to obtain high-quality cDNA libraries from normal and OA tissues, which is necessary to identify protein targets. The latter will be used for the screening of potentially promising compounds.

Several candidate genes have been identified as potential targets for the treatment of OA [95-100], including a wide range of molecules such as cathepsin K, caspases, MMPs and cytokines. Clearly, this field of research and therapeutic development will undergo rapid and probably successful development in the future.

Gene therapy

The current use of gene therapy in the treatment of OA is a result of success in identifying major pathophysiological pathways of the disease process. The principle underlying gene therapy is that disease can be treated by controlling the expression of a number of genes that are responsible for the synthesis of factors involved in cartilage degradation (anti-catabolic) and/or those that promote cartilage repair (anabolic) [101]. The rationale for the use of gene therapy strategies is that, in addition to providing a more effective and sustained delivery of molecules, the molecules are delivered to a precise location. For joint tissues, it has been possible to transfer genes by indirect methods using host cells or by direct transfer using plasmid DNA constructs with different types of carriers to improve efficiency. Until now, gene transfer to synovium has been more successful than gene transfer to cartilage.

A number of natural molecules that can counteract the binding of cytokine to its receptor have been identified. Among these, IL-1Ra (see above) has been extensively tested for its ability to counteract the process of OA. Studies have shown beneficial effects of using different *in vivo* gene therapy strategies with IL-1Ra in two OA experimental models [102,103]. Moreover, the functional genomic of reconstituting human type II IL-1R using gene therapy approaches performed *in vitro* in human and animal chondrocytes showed that reconstitution of type II IL-1R significantly protects cells against IL-1 signalling [104].

A number of strategies that are capable of stimulating cartilage anabolism and joint repair have been tested. These include the use of growth factors such as members of the transforming growth factor-β family, insulin-like growth factor-I and fibroblast growth factor, which were demonstrated to stimulate the formation of hyaline cartilage-like repair tissue. It is therefore conceivable that the transfer of these genes into OA joint cells, such as the chondrocytes, may represent an interesting therapeutic DMOAD option to repair cartilage lesions. However, although growth factors may be successful in repairing cartilage defects in young individuals, they may not be sufficient to repair the damage resulting from years of degradative processes occurring in OA, in which older cells are not responsive to several growth factors, or other factors interact with them. Moreover, the use of growth factors in the treatment of OA is a challenging avenue of research, with several problems still to be addressed; among them are the effects of some of the growth factors on the formation of osteophytes and on their inability to counteract the action of a number of catabolic factors. Until we control the degradative process and know what prevents endogenous growth factors from adequately repairing the cartilage, therapy using growth factors may not be totally successful.

Conclusion

This review summarizes some of the knowledge we have today about the possibility of achieving therapeutic interventions that can modify the natural course of OA. The number of options currently available are clearly quite limited. However, with major advances in our understanding of the disease process and with the recent development of new technologies that can be used to assess and quantify the evolution of structural changes in OA accurately, all of the elements to successfully develop new and effective DMOADs are now in place. It is now just a matter of time before a definitive cure for OA is found.

Competing interests

The authors declare that they have no competing interests.

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