New horizons in osteoarthritis

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Summary

Osteoarthritis (OA), also known as degenerative joint disease, is the most frequent chronic musculoskeletal disease and the leading cause of disability in elderly persons. There are currently at least 27 million persons afflicted with OA in the United States, and the annual cost to society in medical care and wage loss is expected to reach nearly $100 billion dollars by 2020, with consequent increased spending on its diagnosis and treatment, side effect prevention, and loss of productivity. Despite this enormous burden, many aspects of OA are still unknown, with implications not only in terms of diagnosis and assessment but also with regard to therapy. Awareness of this state of affairs has attracted many researchers to this field, making OA one of the most actively studied sectors of rheumatology. Although some clinicians are unaware of recent advances, there is a large body of publications indicating that much has been achieved. Major progress has been made in formulating better definitions of risk factors, in particular in indicating the responsibility of biomechanical and genetic factors, and, with regard to pathogenesis, underlining the role of subchondral bone, cytokines and proteinases. Assessment of OA activity and its progression has been improved with the advent of biomarkers and new imaging procedures, in particular sonography and magnetic resonance imaging (MRI), but also of better clinical instruments, including more reliable patient questionnaires. Information from ongoing studies may improve the to some extent incomplete definition of OA phenotypes. Finally, promising new horizons have been opened up even with regard to the treatment of OA, which is still for the most part unsatisfactory except for surgical replacement therapy. Numerous new substances have been formulated and the findings of trials studying their effects are encouraging, although much has yet to be done.

Key words: osteoarthritis; cartilage; biomechanics; cytokines; proteinases; biomarkers; IL-1; therapy

Introduction

Osteoarthritis (OA) is the most frequent chronic musculoskeletal disease and is undoubtedly by far the most common cause limiting the daily activities of the elderly population [1]. There are currently at least 27 million persons afflicted with OA in the United States, costing the economy approximately $60 billion annually [2, 3]. The annual cost to society in medical care and wage loss due to arthritis is expected to reach nearly $100 billion dollars by 2020, with consequent increased spending on diagnosis and therapy, side effect prevention and lost earnings. At present, approximately 40% of adults aged over 70 suffer from OA of the knee, of these 80% suffer from limitation in movement and 25% are impaired in carrying out their daily activities [4]. It is also important to underline the synergistic effects of other conditions coexisting with OA, in particular obesity and cardiovascular diseases [5, 6].

Despite this enormous burden, OA has not received adequate attention from civil authorities and clinicians, including rheumatologists themselves. An increasing number of researchers have, nevertheless, been attracted to this in some respects “unpopular” field. The reason for this incongruence may at least in part be explained by the presence in the past of a series of misconceptions such as an epidemiologic approach for the most part focussing on the patient’s radiographic profile rather than on clinical characteristics and phenotypes, excessive attendance to traditional radiographic signs, which in this case often become evident only late in the disease’s progression, inadequate exchanges between basic researchers and clinicians on scientific findings and patients’ needs, and limited therapeutic alternatives that have frequently proved disappointing. Awareness of these inconsistencies may perhaps facilitate the search for untired paths aiming to uncover new data clarifying unresolved questions such as the role of risk factors, fostering early diagnosis even in the pre-radiological phase, identifying reliable disease activity indices and, finally, verifying new therapies. Some of these
objectives are close to attainment, as demonstrated by numerous findings published in the literature and outlined in this review.

Risk factors

OA, classified as primary or idiopathic, usually develops without known cause. An increasing body of evidence suggests that some risk factors such as genetic predisposition, age, obesity, female sex, greater bone density, joint laxity, and excessive mechanical loading may play a part in its development. Although age is the most important risk factor in OA it is still unclear whether it should be considered an ageing process or a “true” disease, since the former occurs in all members of the population while the latter affects only a limited subset [7, 8]. In addition, despite the fact that almost all elderly people show radiographic findings of OA, the number of subjects who actually complain of symptoms directly related to the disease is much lower [9, 10].

Biomechanics is the term commonly used in OA to define the biochemical reaction to mechanical stimuli, a process considered crucial for the disease’s modern pathogenesis. Joint structures are organised for functions essentially related to biomechanical reactivity [11].

EHOA, a severe subtype of hand OA, and an SNP on gene encoding IL-1β [12], were found between variations in IL-1β and IL-1Ra production and JSN progression. The innate capacity to produce TNFα and IL-10 upon LPS stimulation is thus associated with radiological progression of knee OA, even over a relatively long period [13]. The adverse effects of joint malalignment and congruity in these patients may contribute to the possible loss of articular cartilage and in some cases early OA onset [14, 15].

Joint space narrowing (JSN) was present 24 months after baseline in 33.7% of symptomatic patients with knee OA [16]. A recent analysis of x-ray features of hand and knee OA in twins recruited from a healthy population demonstrated that genetic factors accounted for between 39% and 65% of the variation in liability to disease at these two sites [17].

With regard to the most important susceptibility genes recently identified, frizzle-related protein 3 (FRZB) [18] and asporin (ASPN) [19] are particularly interesting. Studies carried out in the UK have reported that two single nucleotide polymorphisms (SNP) of FRZB increase the risk of knee and hip OA in Caucasian women but not in men [20, 21]. SNP’s role was not confirmed in a Spanish population, in which another SNP tended to be more frequent in patients with clinical disease in multiple joints, and specifically in women with hip OA [22, 23].

Many of the gene defects affecting the formation of the cartilage matrix and patterning of skeletal elements during development result in a variety of congenital cartilage dysplasias with Mendelian inheritance, though occurring only very rarely [24]. Interestingly, OA is most often site-specific in individuals with skeletal dysplasias. Mutations in the type II collagen gene (COL2A1), for example, cause spondyloepiphyseal dysplasia congenita. Although this cartilage-specific collagen is the most abundant component of articular cartilage in all joints, the OA phenotype of the disease is sitespecific [25]. Hip OA is very severe, spine and knee OA is moderately severe, but the hand is normal. Mutations in COMP (cartilage oligomeric matrix protein), another abundant component of articular/epiphyseal cartilage, cause early, severe OA but the spine and peripheral joints are unaffected [26]. The adverse effects of joint malalignment and congruity in these patients may contribute to the possible loss of articular cartilage and in some cases early OA onset [27].

Genetic predisposition may also influence the type of reactivity of some innate functions involved in the inflammatory response. Botha-Scheepers et al. have demonstrated that joint space narrowing (JSN) was present 24 months after baseline in 33.7% of symptomatic patients with knee OA [28]. After stimulation of whole blood samples with lipopolysaccharide (LPS) it was found that patients in the highest quartile of tumour necrosis factor (TNF)α production had a sixfold increased risk while patients in the highest quartile of interleukin (IL)-10 production had a fourfold increased risk of JSN progression, as compared, in both cases, with values in patients in the lowest quartile [29]. No significant associations were found between variations in IL-1β and IL-1Ra production and JSN progression. The innate capacity to produce TNFα and IL-10 upon LPS stimulation is thus associated with radiological progression of knee OA, even over a relatively short follow-up period of 2 years. Another study by the same group produced similar results. In the Genetics of Osteoarthritis and Progression (GARP) study, the role of the C-reactive protein (CRP) gene in hand OA (HOA) was evaluated by determining serum levels of CRP using a high sensitivity (hs) method and assessing genetic variations of the CRP gene by genotyping five tagging SNPs [30]. A haplotype of the CRP gene, linked to a high basal hsCRP level, was associated with severe HOA, indicating that innate high basal serum-hsCRP levels may influence OA onset and severity [31].

Another interesting study by Stern et al. supports the hypothesis of a genetic association between erosive hand OA (EHOA), a severe subtype of hand OA, and an SNP on gene encoding IL-1β [32].

Biomechanics is the term commonly used in OA to define the biochemical reaction to mechanical stimuli, a process considered crucial for the disease’s modern pathogenesis. Joint structures are organised for functions essentially related to
Cytokines, growth factors and metalloproteinases

Cytokines, involved in cell-cell interactions, are hormone-like proteins that regulate the intensity and duration of the immune response [43]. Cytokines and growth factors involved in OA may be released from different cellular sources, such as chondrocytes, synovial cells or osteocytes. It is almost certain that cytokines are involved in OA development and progression, and that blocking cytokines is useful in protecting cartilage from damage [44–46].

IL-1 and TNF are the most important and best studied cytokines in OA. IL-1, released either by the synovium [47] or the chondrocytes [48], could stimulate the latter to produce most or all of the proteinases involved in cartilage destruction [49, 50]. TNFα and IL-1 may also inhibit the synthesis of proteoglycans and type II collagen [51, 52]. Chondrocytes in OA cartilage express IL-1, IL-1β converting enzyme (caspase-1) and type 1 IL-1 receptor (IL-1R) [38]. In turn, IL-1 synthesised by chondrocytes may be able to induce the expression of MMPs and aggrecanases [51, 52], the synthesis of prostaglandin E2 (PGE2) [53, 54] and the production of nitric oxide (NO) via inducible NO synthetase (iNOS, or NOS2) [48, 55, 56]. IL-1β also induces other proinflammatory cytokines such as IL-6, leukaemia inhibitory factor (LIF), IL-17, and IL-18 and chemokines, including IL-8 [38, 57]. IL-6 plays an important role in influencing cartilage metabolism. When Guerne et al. analysed the effects of IL-6 on proteoglycan synthesis by human articular chondrocytes in the presence of sIL-6R [58], they found that sIL-6R potentiates the inhibitory effect of IL-6 on proteoglycan synthesis by articular chondrocytes, but the overall effect of IL-6 + IL-6sR is moderate compared to that of IL-1 [58].
Cytokines involved in cartilage metabolism can be grouped into three categories: catabolic cytokines, which include IL-1β, TNFα, IL-17, and IL-18; inhibitory cytokines, which include IL-4, IL-10, IL-11, IL-13, IL-1 receptor antagonist, and interferon-γ; and anabolic cytokines, which comprise insulin-like growth factor 1, TGFβ1, TGFβ2, TGFβ3, fibroblast growth factor (FGF)-2, FGF-4, FGF-8, BMP-2, BMP-4, BMP-6, BMP-7, BMP-9, and BMP-13 [46].

Cytokines synergise with one another in closely integrated processes in OA and may affect disease progression and pain. Angiogenesis may promote chondrocyte invasion of bone marrow tissue into this region [79]. In any case, it is possible that a crucial role is played by the vascular production of bone-derived products, cytokines, and MMPs [75]. Among the members of the MMP family relevant roles are played by MMP-13, involved in the degradation of collagen type II in OA cartilage [67], and by ADAMTS4 and ADAMTS5, believed to be key proteases in the degradation of aggrecans [69, 70].

**Adipokines**

The term “adipokine” is generally applied to biologically active substances found in the adipocytes of white adipose tissue (WAT), although they may be synthesised at other sites too [71]. Adipokines include a variety of pro-inflammatory peptides or cytokines which contribute to the “low-grade inflammatory state” of obese subjects [72, 73]. The best known of this family are leptin, adiponectin and resistin. Leptin is a 16 kDa non-glycosylated peptide hormone belonging to the class I cytokine superfamily chiefly produced by adipocytes [74]. Leptin can be considered a cytokine-like hormone with pleiotropic actions exerting biological influences by binding to its receptors [75]. Leptin is able to modulate cells involved in immune/inflammatory reactions, including monocytes/macrophages, neutrophils, dendritic cells and T-cells [76].

Leptin production is much higher in OA human cartilage than in normal cartilage [72]. The finding that administration of exogenous leptin increases IGFI and TGFβ1 production by rat knee-joint cartilage has suggested that high circulating leptin levels in obese individuals may protect cartilage from degeneration [77]. Under pathological conditions, however, control of matrix homeostasis by chondrocytes in the joint is lost. In cultured human and murine chondrocytes, NOS2 activation by IL-1 is increased by leptin via a mechanism involving JAK2, PI3K, MEK1 and p38 [78]. It has recently been demonstrated that leptin is also able to induce synthesis of relevant MMPs involved in cartilage damage, such as MMP9 and MMP13 [79].

Adiponectin is produced largely by WAT and has structural homology with collagens VIII and X and complement factor C1q [80]. Adiponectin acts via two receptors, one (AdipoR1) found predominantly in skeletal muscle and the other (AdipoR2) in the liver [81]. Adiponectin has a wide range of effects in immune and inflammatory diseases and exerts relevant actions on innate and adaptive immunity [71]. In contrast to a “protective” role against obesity and vascular diseases, it seems that in skeletal joints adiponectin may be proinflammatory and involved in matrix degradation [79]. Chondrocytes present functional adiponectin receptors, activation of which leads to the induction of NOs2 via a signalling pathway involving PI3 kinase; and adiponectin-treated chondrocytes similarly increase IL-6, TNF and MCP1 (monocyte chemotactic protein 1) synthesis [82].

Resistin is a dimeric protein that received its name from its apparent induction of insulin resistance in mice, thus providing a possible link between obesity and insulin resistance [83]. Levels of both resistin and leptin are elevated in obese individuals. Resistin is produced by WAT and monocyte/macrophages, but also by cartilage itself, and is a very powerful proinflammatory cytokine, increasing production of IL-1, TNF-α, and various chemokines [84]. Following traumatic joint injury, resistin levels are increased, causing matrix degradation and release of inflammatory cytokines from articular cartilage [85].

Serum levels of adiponectin and resistin were recently measured in 48 women with erosive HOA (EHOA), 27 with non-EHOA and 20 without HOA as controls [86]. Adiponectin but not resistin were significantly higher in EHOA than in non-EHOA or healthy controls. Both adiponectin and resistin neither correlated with the levels of CRP nor were related to Body Mass Index, thus suggesting that adiponectin may play a role in the pathophysiology of the erosive subset of HOA [86].

**Subchondral bone**

An increasing body of evidence shows that subchondral bone is actively involved in the pathogenesis of OA through several possible mechanisms, including a defect in its role as a shock absorber; abnormal osteocyte function; increased production of bone-derived products, cytokines, and MMPs [38, 62, 63]. It is still unclear whether changes occurring in subchondral bone precede or follow OA onset. In any case, it is possible that a crucial role is played by the vascular invasion of bone marrow tissue into this region [87]. In agreement with this, it has been seen that concentrations of some inflammatory cytokines such as IL-1, TNF and IL-6 are significantly upregulated, supporting the hypothesis that vascularised subchondral plates may increase the synthesis of cytokines and proteolytic enzymes, thereby contributing to the degradation of adjacent hyaline cartilage [88].

The importance of angiogenesis in OA has recently been discussed in detail [89]. Angiogenesis and inflammation are closely integrated processes in OA and may affect disease progression and pain. Angiogenesis may promote chondrocyte hypertrophy and endochondral ossification, contributing to radiographic changes in the joint. In association with
inflammation it may sensitisve nerves and thus increase pain. Innervation may also accompany vascularisation of the articular cartilage, where compressive forces and hypoxia may stimulate these new nerves.

Several experiments have demonstrated that inadequate fluid flow round osteocytes may result in osteocyte apoptosis, attraction of osteoclasts and excavation of the nonviable bone [90, 91]. In some cases partial or total collapse of subchondral bone may take place, as can be seen in avascular necrosis (AVN) [87, 92]. Subchondral bone ischaemia may be crucial to OA development in several ways, first of all by blocking the nutrient and oxygen supply, usually furnished by the dense subchondral vasculature in close proximity to the cartilage, and via microchannels that penetrate the subchondral mineralisation zone, permitting communication between bone and cartilage [87].

These events at the subchondral bone level are clearly demonstrated by high resolution magnetic resonance imaging (MRI) of the joints. Bright areas of subchondral bone on MRI, commonly observed in both early and established OA and in individuals with painful joints [92], probably correspond to areas of bone marrow-like oedema lesions (BMLOL), occurring idiopathically or in response to bone trauma [93]. Longitudinal studies have shown that BMLOL is an important risk factor for structural deterioration in knee OA [94–96]. It has recently been shown that subchondral cysts, characteristic of established and severe OA, develop in preexisting regions of subchondral BMLOL [97]. While BMLOL’s origin is unknown, it may be secondary to ischaemic episodes perhaps exacerbated by reperfusion injuries [98, 99].

Biomarkers

Molecular markers in OA have been the object of growing attention due to their potential usefulness in formulating early diagnosis, in assessing disease activity and severity and in evaluating drug effects [109]. In this respect, biochemical markers or biomarkers are ideal, as they are non-invasive and inexpensive measures [101]. The NIH-funded Biomarkers Network, a multidisciplinary group interested in the development and validation of biomarkers, has recently proposed the “Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic” (BIPED) biomarker classification [102]. It may be concluded, however, that although a great number of substances are continually proposed, only a few can be considered true OA “disease markers” [100–108].

Until now no biomarkers appear to have been able to assist in OA disease diagnosis in the preradiological stages, but with the recent introduction of highly sensitive (hs) immunoassays, a growing number of studies have suggested that CRP may be a marker of OA activity and severity [106]. It would seem that higher CRP levels may predict worse disease outcomes over the next four years [109].

It has been observed that serum hsCRP levels are higher in patients with EHOA than in non-EHOA patients [110]. This probably reflects disease activity rather than subtype, since hsCRP levels correlate with clinical activity scores [110]. As MMPs are particularly involved in cartilage degradation, their levels or activities have been investigated in an attempt to obtain information concerning OA severity or progression [111]. The most abundant MMP both in serum and SF is MMP-3 [111, 112]. It has been hypothesised that pro-matrix MMP-3 acts as a marker for posttraumatic cartilage degradation [113, 114].

The molecular markers most useful in identifying cartilage synthesis or degradation originate from different articular sources such as cartilage, bone and synovial tissue [101, 102]. Serum hyaluronan (HA), a marker of synovial proliferation and hyperactivity, appears to reflect OA progression [115, 116]. Other interesting biochemical markers are serum keratin sulphate (KS), COMP, YKL-40, and urinary C-terminal crosslinking telopeptides of collagen types I and II (uCTX-II) [106]. COMP concentrations in synovial lavage fluids as well as in serum are an early indicator of radiographic progression at follow-up [117–119]. It has also been seen that COMP is the most sensitive test for identifying subjects affected with the genetic form of premature OA [120, 121]. In the ECHODIAH study, performed by French investigators to determine whether systemic markers of bone, cartilage, and synovium can predict structural progression of hip OA, 10 markers were evaluated: N-propeptides of collagen types I and III, COMP, YKL-40, HA, MMP-1 and MMP-3, CRP and urinary C-terminal crosslinking telopeptides of collagen types I and II (uCTX-II) [122]. Combined measurements of uCTX-II and sHA were found to be the best predictor of structural progression in hip OA [122]. Coll 2-1 and Coll 2-1 NO2, new serum biochemical markers, have recently been used to study oxidative-related type II collagen network degradation in patients with OA and RA [123]. No relationship was found between radiological OA severity and serum levels of these markers, but, interestingly, Coll 2-1NO2 was correlated with CRP in the sera of OA and RA patients [123]. Coll 2-1, Coll 2-1NO2 and myeloperoxidase (MPO) were all higher in the serum of patients with EHOA than in that of non-EHOA subjects, although only the rise in MPO was significant [124]. In another study, Coll 2-3/4C epitope levels were higher in the EHOA patients than in the nodal non-EHOA subjects and controls [125].

Phenotyping osteoarthritis

In their daily practice clinicians are no doubt frustrated by the bulk of basic research activities concerning OA compared with the few products really available for their patients. The task of clearly defining markers that can be used for early preradiological diagnoses and assessment of disease activity or progression is, on the other hand, quite arduous in the absence of a well-established clinical definition. It must be said that much effort continues to be expended in improving the quality of clinical observation.
In this context an important step was taken by the American College of Rheumatology in establishing criteria for diagnosis and classification of OA with emphasis on the role of pain [126]. Since that time constant advances have been made in the assessment of symptoms and signs, facilitating early diagnoses and, at times, identification of a subtype or variant not yet detectable by means of radiographic or laboratory findings. EHOA, for example, can be identified by assessment of clinical features even before x-ray identification is possible. In fact, this subtype of hand OA is characterised clinically by frequent inflammatory episodes at times persisting for years and, at times, involving several joints simultaneously [127]. By contrast, flares of nodal HOA occur chiefly at the onset of each joint’s involvement, in a “stuttering” onset polyarthropathy of distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints resembling a “monoarthritis multiplex” [127]. Typically, the patient develops discomfort followed by swelling of a single interphalangeal joint, later involving another IP joint and then another, producing the “stuttering onset” of polyarthritis of distal and proximal IP joints. Instability and ankylosis of IP joints are, moreover, almost always a feature only of EHOA [128]. Since EHOA is commonly detected by MRI [129], in future the criteria defining EHOA will probably also include specific clinical features in addition to erosion [130].

In keeping with the idea that the modern approach to OA should include adequate evaluation of affected patients, advancement in disease assessment has been obtained by the use of reliable questionnaires, in particular those evaluating quality of life, function pain and radiographic progression [131–133]. Under the auspices of the OARSI (Osteoarthritis Research Society International) and the OMERACT (Outcome Measures in Rheumatology Clinical Trials) initiative, an international working group was recently set up to define the theoretical requirements for total joint replacement in knee and hip OA for use by clinical trials evaluating potential disease-modifying drugs [134]. It was their decision that the domains of pain, physical function and joint structure on x-rays would be combined as a surrogate measure of outcome [135, 136].

High scores on self-reported health-related quality of life (HRQOL) questionnaires have been found to be associated with higher odds of visiting a physician, using analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), and having had arthroplasty [137]. The relationship between mental health and physical disability is a complex problem particular to OA. It has been demonstrated that the depression commonly found in older persons is associated with functional disability [138], and that depression and pain are more important predictors of disability than radiographic evidence of degenerative joint alterations in patients with hip or knee OA [139]. It has also been observed that treatment for depression, e.g. antidepressants and/or psychotherapy, may reduce pain and improve functional status and quality of life in older patients with OA [140].

It is to be hoped that the availability of these new tools will help to differentiate OA subtypes and improve health professionals’ attitude to their patients.

**Future therapeutic strategies**

One of the most frequent complaints by clinicians treating OA patients is their frustration with the ineffectiveness of the therapeutic tools that are available. As underlined by recent recommendations, one of the reasons for this state of affairs is probably the lack of a global OA management strategy [141–145]. There is no doubt that, with respect to other rheumatic diseases, pharmacological treatment of OA is the least satisfactory. Advances in surgical treatment are much more evident, with regard not only to joint replacement but also to tissue engineering, so-called “biosurgery” [146–147]. These have been linked to space-filling materials, also known as scaffolds, capable of regenerating or repairing cartilage [148]. Cell transplantation has not yet been attempted in the treatment of OA.

Just as in other types of arthritis, and bearing in mind the importance of genetic predisposition, even gene therapy could be a powerful tool for the future. However, it is unlikely that in future strategies modification of relevant gene mutations can be used to treat OA. A more realistic approach may be to try modifying the synovium or subchondral bone to enhance synthesis of the cartilaginous matrix, inhibit its breakdown, or a combination of the two [149–151].

Unfortunately, all the results currently available concern either animal models or in vitro studies, since no human clinical gene therapy trials have been implemented.

A number of ongoing trials are exploring the use of anticytokine therapy. Three strategies currently targeting the activities of catabolic cytokines include: inhibiting the proteinases that degrade cartilage matrix proteins [152], suppressing cytokine-induced signalling pathways [153, 154] and inhibiting chondrocyte apoptosis using inducible NO synthase or caspase inhibitors [155]. As several proteinases involved in OA share overlapping substrate specificities and structural epitopes, some proteinase inhibitors appear to be effective in both animal models and human clinical trials [156]. Kreuzski et al. have, however, recently reported that PG-116800, the MMP inhibitor, is not only ineffective in modifying the matrix structure in OA patients but seems to provoke numerous musculoskeletal adverse effects [157].

Strategies to suppress cytokine-induced signalling pathways include: cytokine neutralisation, receptor blockade, inhibition of cytokine processing, inhibition of cytokine synthesis or action, and combined therapies [44, 158].

In ongoing trials drug administration is primarily through oral and infusion therapy and is only rarely intraarticular. It is possible that some factors may limit the efficacy of anti-cytokine drugs administered by this latter pathway, including a shorter half-life. This is probably the reason why anakinra, the IL-1 receptor antagonist, was found to be effective in modifying disease progression in animal models [159, 160] and in a 12-week open-label study on symptomatic human knee OA [161], but caused no statistical improvement over placebo after one month in a follow-up controlled trial [162].
In a prospective randomised controlled trial autologous interleukin-1 receptor antagonists were however found to improve function and symptoms in OA patients compared to placebo [163].

The intraarticular pathway has in any case proven to be a satisfactory tool for patients and physicians alike, as demonstrated by the fact that, together with hyaluronate derivatives, it has won worldwide popularity [164–168]. Many pharmaceutical companies are in fact anxious to accelerate research in this area, as demonstrated by the many interesting products now being tested in animals and in phase I human trials.

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