Osteoarthritis Treatment Evolution from Symptomatic to Disease-Modifying Strategies

Jean-Pierre Pelletier, MD and Johanne Martel-Pelletier, PhD
University of Montreal Hospital Center-Notre-Dame Hospital
Osteoarthritis Research Unit
Montreal, Quebec, Canada

Over the last decade, there have been several interesting advances in the treatment of osteoarthritis (OA). A clearer understanding of the pathophysiology of this disease (1) has facilitated the development of new approaches for treatments aimed at specifically and effectively retarding disease progress. New classes of molecules that inhibit one or more OA catabolic processes are under evaluation for their potential to alter the degenerative process.

Osteoarthritis can be described as the degradation and loss of articular cartilage accompanied by subchondral bone remodeling, osteophyte formation, and synovial membrane inflammation. This is clinically reflected by a gradual development of fluctuating joint pain, swelling, stiffness, and loss of motion. The pharmacological interventions in OA have focused on treating pain primarily using NSAIDs, analgesics and, more recently, specific cyclooxygenase-2 (COX-2) inhibitors. The rationale behind this type of pharmacological intervention was to inhibit COX, the key enzymes that metabolize arachidonic acid into prostaglandins (PG).

Clinical studies to date have focused on the alleviation of signs and symptoms, for which comparable efficacy has generally been demonstrated for NSAIDs and acetaminophen in stable cohorts of patients with mild-to-moderate OA (2, 3). Published data on intra-articular corticosteroids in OA have demonstrated short-term (up to 4 weeks) improvement of signs and symptoms compared with placebo (2, 4). The comparative efficacy of these agents in the treatment of episodic crystal-induced inflammatory exacerbations superimposed on chronic OA in selected patients (5), in which one might predict superior efficacy for NSAIDs or corticosteroids over acetaminophen, has not been studied. However, the main objectives in the management of OA are not only to reduce symptoms and minimize functional disability, but also to limit progression of structural changes.

Since there are in vitro data to indicate that corticosteroids inhibit synoviocytes and chondrocyte production of interleukin-1 (IL-1), COX-2, and tumor necrosis factor-α (TNFα) (4), there has been speculation that intra-articular corticosteroid administration could exert a disease-modifying role in OA. However, a recent structural outcome study in humans has not been able to validate such a hypothesis (6). Similarly, despite speculation that NSAIDs exert beneficial or harmful effects on the integrity of articular cartilage, there are no validated imaging studies that shed light on this controversy. Predicting the net effects of COX inhibitors on cartilage structure is particularly difficult given the observed pleiotropic effects of individual eicosanoids in vitro on chondrocyte functions as discussed above. Thus, although the long-term effects of available anti-inflammatory agents on cartilage merit further investigation, there is significant interest in new agents that have the potential to reduce or stop the progression of structural changes observed in OA. Such agents offer great promise and are likely to lead to very significant changes in therapeutic approaches in the near future.

In that regard, the most attractive recent findings are the data pointing to an association between inflammation and disease appearance and progression (7). In fact, there are several studies in which the levels of biomarkers such as cartilage oligoprotein (COMP), hyaluronic acid (HA), or C-reactive protein (CRP) were measured in OA patients. These studies have demonstrated that there is a strong correlation between synovial inflammation and OA progression as well as an association with strong risk factors. It is generally believed that clinical signs reflective of an active disease suggest the likelihood of rapid progression of the disease. Moreover, there are a number of pathways linked to inflammation, which represent the most interesting therapeutic targets. For instance, cytokines, such as IL-1β and other pro-inflammatory cytokines or inflammatory factors,

are likely responsible for the signs and symptoms of inflammation present in OA patients. There exists a number of ways by which the production or activity of cytokines could be reduced. The action of cytokines can be reduced at the cell membrane level by decreasing the membrane receptor level or by the use of receptor antagonists or soluble receptors. The action of the cytokine can also be reduced by blocking the intracellular signaling pathways.

We have demonstrated that the natural IL-1 receptor antagonist (IL-1Ra) is capable of reducing several cartilage catabolic processes, which are IL-1β dependent. Indeed, in vivo studies in animal models have demonstrated that the intra-articular injection of IL-1Ra could block the action of IL-1β and reduce disease progression (8). Studies using gene therapy and different gene transfection methods have allowed for the successful in vivo transfection of the IL-1Ra gene into the OA knee joints of dogs and rabbits (9, 10). These studies have also demonstrated that such therapeutic intervention could reduce the progression of OA lesions.

Another interesting target for controlling the activity of the IL-1 system is the IL-1 converting enzyme (ICE)/caspase-1, an enzyme which is responsible for the conversion of the proform of IL-1β into its active (mature) form (11). There are a number of studies already underway in rheumatoid arthritic patients with an orally active ICE inhibitor. Certainly, this form of therapy also represents an interesting potential target for the treatment of OA.

The role of proteases in the degradation of the extracellular matrix of cartilage in OA has been well documented, and metalloproteases (MMPs) are believed to play a major role in this process. Inhibition of the synthesis/activity of these enzymes as a treatment for OA has been the focus of intensive research (12). To date, the most promising strategy is the use of chemical molecules that can block the activity of MMPs. Certain MMPs, such as MMP-13, have been selected as being the most attractive targets for the treatment of OA. The main reason(s) for choosing selective inhibition, instead of a broad inhibition, is based on the hypothesis that by doing so we can avoid a certain number of side effects that could potentially be related to a broad MMP inhibition. MMP action can be controlled in a number of ways, mainly by inhibiting their synthesis or the transformation of the proMMPs into active MMPs. The enzyme activity per se could be inhibited in many ways, including through the use of chemical inhibitors. Generally, these chemical inhibitors are chelators of heavy metals such as zinc and calcium. A number of these compounds that have a broad range of MMP activities have already been tested in clinical trials. From these trials, we have learnt that MMP inhibitors could produce side effects and have not yet demonstrated a major reduction in the progression of the disease.

Another possible way to count the effect of certain catabolic factors lies in the inhibition of certain intracellular signaling pathways such as the protein kinase cascades. They are responsible for transmitting the signal induced by the binding of the ligand to its receptor from the cell membrane to the nuclei, where it induces the cell response. The inhibition of kinases which constitute the most appealing targets include p38, ERK 1/2 and SAPK/JNK. There are already a number of drugs under development targeting the specific inhibition of these kinases. In one of our recent studies (13), we showed that orally active ERK 1/2 selective inhibitors could very significantly and effectively reduce the progression of lesions in the rabbit OA model, and, as well, reduce the synthesis of catabolic factors which are ERK 1/2 dependent, such as MMP. Moreover, another emerging field of research focuses on the development of molecules that can inhibit the binding of transcription factors at the DNA level. The major transcription factor targets for cytokines and MMPs are NF-kB and AP-1.

Among the different catabolic pathways activated by inflammation, nitric oxide (NO) is an interesting one in the context of OA for at least two main reasons. First, NO and its byproducts are capable of inducing the inflammatory component of OA. Second, they are also capable of inducing tissue damage and tissue destruction and, therefore, could be responsible not only for symptoms but also the disease process per se. It has been shown that the excess production of NO generated via an elevation of inducible NO synthase (iNOS) in OA tissues is injurious. This appears to occur through a number of mechanisms. To begin with, NO could induce chondrocyte death by apoptosis. It could also stimulate the synthesis and activities of MMP, and reduce the anabolism of cartilage by inhibiting the synthesis of the major matrix components — collagen and proteoglycan. Moreover, NO is capable of increasing the activity of COX-2 and consequently appears responsible for an increase in the signs and symptoms of the disease. Therefore, it is believed that this molecule is a most interesting target, because reducing its excess production may not only reduce the symptoms but also may likely reduce the progression of disease, making it able to reach two targets simultaneously. This hypothesis is supported by positive findings in recent studies done using the experimental dog model of OA and the oral administration of therapeutic dosages of a specific inhibitor of iNOS (14, 15).

OA structural changes also involve modifications in the morphology of the surrounding bone. Subchon-

dral bone remodeling is a well-recognized manifestation of OA. New data underline the concept that abnormal subchondral bone cell functions may contribute to the onset/progression of OA. Recent work suggests that very early in the OA process, biological and morphological disturbances occur at the subchondral bone and may have a role in the modulation of articular cartilage metabolism. Therapeutic effects of drugs that prevent the abnormal metabolism of subchondral osteoblasts on the progression of OA lesions is of major interest in the context of future intervention.

This review has brought to light the most recent progress in the understanding of pathophysiology of OA. Several interesting new approaches for the treatment of this disease are now being explored. New classes of molecules that inhibit one or more of the disease processes of OA are under evaluation for their potential to alter the degenerative process.

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