

## Osteoarthritis: New Perspectives

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Osteoarthritis (OA) is the most common and frequent disease in rheumatology. Aging and obesity are the two main risk factors linked to OA, and because of the aging population and the increasing rates of obesity, the number of OA patients stands to increase dramatically. To date, 46 million adults in the United States—more than 50 percent of adults aged 50 and over—have been diagnosed with OA: it is predicted that by the year 2030, that figure will rise to around 70 million [1].

In the last two decades, many mechanisms have been discovered about this disease. Cartilage, which previously was considered inactive tissue, is now actively studied as the main active tissue of joints; it is being studied as part of the whole joint, including other tissues as subchondral bone, synovium and tendons. OA mainly targets the major joints (knee, hip, and back) but commonly affects the hands, elbows, and ankles. Osteoarthritis is a degenerative disease caused by the loss of cartilage and inflammation: it is often—but not always—accompanied by pain and sometimes occurs subsequent to an injury as primary or secondary OA. The disease results in an imbalance between catabolic and anabolic factors in cartilage. Chondrocytes, osteoblasts, and synoviocytes seem to cross-talk and be part of the process. Current molecular and genetic approaches have led to the identification of more complex mechanisms.

The practical questions this paper addresses are: how should we treat OA in the next 10 years, and how can we help aging patients manage their arthritis?

Although the ultimate goal for the treatment of OA would be to halt the disease progression and restore cartilage damage and relieve pain, effective cures are not currently available and recommendations for treatment vary. The European League Against Rheumatism (EULAR), the OsteoArthritis Research Society International (OARSI) and the American College of Rheumatology (ACR) have developed various recommendations for treating OA, depending on its location [2-8].

Roddy and Doherty have written a critical review of EULAR's and ACR's recommendations for treating OA, which are generally similar, combining non pharmacological and pharmacological approaches [9]. Rannou et Poiraudau recently published an exhaustive list of nonpharmacological treatments for OA, echoing the work done by Felson et al. [10] on malalignment: treatment regimens range from orthosis to exercise, patient education, and diet, depending on OA location [10-13]. The recent study by Richette et al. [14] concerning obesity and diet and OA highlighted the importance of such non pharmacological treatments [14]. Briefly, non pharmacologic treatment include orthosis (such as using insoles and specific shoes, depending on the location), moderate exercise (specific postural exercises, swimming, walking), acupuncture, thermotherapy, and walking aids such as canes crutches, frames, wheeled walkers, and walking sticks. Diet and weight loss are also recommended, although these are a challenge and a difficult process for obese patients. Defining a weight objective could lead to improvement not only with OA but also with metabolic and cardiovascular diseases. No matter the recommended treatment, education and information are vital for effecting patient compliance. Physicians and therapists play an important role in providing such education during time spent with their patients: regular phone calls may help as well.

The pharmacological approach for the treatment of OA differs from Europe to the U.S., although both approaches share the common

goal of managing pain while also managing disability. Pharmacological guidelines for the management of OA recommend acetaminophen up to 4g/day as first-line therapy. Alternative pharmacological therapy should be used only in the presence of an inadequate response and severe pain. If acetaminophen cannot control symptoms or if inflammation signs are detected, the use of NSAIDs at the lowest dose is recommended, with consideration of a gastro-protective agent. OARSI and EULAR guidelines recommend that if patients don't respond to oral analgesics, they should receive intra-articular injections of either corticosteroids or hyaluronate followed by the use of opioids and narcotics only when all other pharmacological options have been considered. Surgery, including joint replacement, is recommended only as the last option [15]. Finally, the use of topical NSAIDs, capsaicin, and SYSADOA (SYmptomatic Slow-Acting Drugs for OA, which includes avocado/soybean unsaponifiables (ASU), chondroitin, diacerein, and glucosamine) is recommended by EULAR and OARSI.

### Which Treatment for the Future?

The search for new treatments and possible molecules targets has raised a number of important questions: Does the disease start in the cartilage or in the subchondral bone? [16] What comes first, altered mechanical loading, bone sclerosis, or cartilage degradation? [17-19] Recent discoveries have shown that subchondral bone is involved in OA pathophysiology, [20] which raises further questions: If subchondral bone initiates OA, what initiates bone imbalance? This question finds its analog in other diseases: What initiates cancer? Further questions logically follow: is OA a single disease? The comparison of OA of the hands, spine, hip, and knee shows a multiple factorial disease. When we look closer again, we can spot an intricacy of the different tissues. Subchondral bone contains a rich and huge vasculature. Moreover, hip and knee OA are largely studied, but what about hand OA? The problem of obesity and metabolic syndrome has led to a reconsideration of the factors involved in hand OA [21]. Differences in gender, genetic factors, age, and previous injury have been shown to play a role as well. Will only one Disease Modifying OsteoArthritis Drug (DMOAD) work? Is there a single "magic bullet" therapy, or is a combination therapy more effective? Dexamethasone, a glucocorticoid treatment that abolishes pro-inflammatory cytokines and injury defects, is one example of a therapy with a double target [22]. While imagining new identified targets with specific inhibitors, as signaling pathways, MMPs, chromatin modifying enzymes, we could ask: Could we cumulate all the new inhibitors? The molecular network in OA is well interconnected and the balance between the different

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mechanisms is fragile. Disturbing a mechanism in trying to balance a pathologic pathway could lead to imbalance in another pathway—which is precisely what happened with MMP inhibitors years ago [23].

A brief review of the current new molecules in clinical development shows two main targets: pain and structural modification [24]. Targeting pain, we can cite 5 anti-NGF (Nerve Growth Factor) humanized antibodies (i.e., Tanezumab), a 5-LOX (lipoxygenase) inhibitor, a PG (Prostaglandines) inhibitor, NSAID, a Hyaluronic Acid (HA), and an HA combined with steroids. Targeting the structural modification, we can cite a pro-anabolic growth factor (BMP-7), a salmon calcitonin for bone and articular surface preservation, a MAP (Mitogen Activated Protein) kinase inhibitor, an iNOS (Nitric Oxide Synthase) inhibitor, a pro-anabolic growth factor, FGF-18, an anti-IL1 antibody, Canakinumab, a pro-anabolic and anti-inflammatory autologous bone marrow stem cells process, and an IKK (Inhibitor of Kappa Kinase) inhibitor. The modality of drug delivery also needs to be considered: locally versus systemic (IA, IV, oral, topic) [24] OA has multiple etiologies and interconnecting pathways, so targeting only one molecule does not seem the solution to effectively treating OA: the single compound for treating OA will most probably never exist.

In conclusion, all these questions—about the initiator of the disease, the different targets, the differences between OA locations, and aging and obesity mechanisms—have not yet found definitive answers and remain to be elucidated before planning new therapeutical designs for treatment of OA in the future. Discovering the precise role of subchondral bone or cartilage and identifying a precise order of events happening in the pathology remain the first challenges of the future decade. Meanwhile, much can be done already to treat this multifactorial disease with a variety of simultaneous treatments and common sense—particularly dealing with obesity, which has become the challenge of the future decade.

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