Recent Developments in the Therapy of Osteoarthritis

Jean-Pierre Pelletier
and Johanne Martel-Pelletier

CONTENTS
INTRODUCTION

INTRODUCTION

The last decade has been the scene of several interesting advances in the treatment of osteoarthritis (OA). Improved understanding regarding the pathophysiology of OA has contributed to the development of new strategies for treatments aimed at specifically and effectively retarding or stopping the progression of this disease.

The drugs in development for the treatment of OA can be classified as being either symptomatic or structure (disease)-modifying. Greater comprehension of the mechanisms responsible for joint damage and repair has led to the development of several new classes of molecules that inhibit one or more OA catabolic processes, whereas some of the drugs now used are being evaluated for their potential to alter the degenerative process.

Although nonsteroidal antiinflammatory drugs (NSAIDs) are effective for acute and chronic pain, their use in the treatment of OA is not completely resolved. Some of the hesitation regarding the use of NSAIDs for the treatment of OA is related mainly to their side effects. A significant level of gastrointestinal (GI) complications have been well-documented and are related in part to the local inhibition of prostaglandin synthesis. NSAIDs appear to share some degree of similarity, in that they inhibit prostaglandin synthesis, which are produced by cyclooxygenase (COX). At least two isoforms of this enzyme have been identified: COX-1, which plays a constitutive role, and COX-2, which plays a critical role in the inflammatory disease process. The recent discovery of these isoforms has allowed the synthesis of a new generation of drugs that specifically block COX-2 but spare COX-1. These anti-inflammatory drugs have proven to be much safer compared to the classic NSAIDs, which inhibit both COX-1 and COX-2. The new specific COX-2 inhibitors have so far fared as well as the old ones in terms of efficacy in OA. It is hoped that these new NSAIDs will have a better risk-to-benefit ratio than classic NSAIDs, given their lower morbidity toward the GI tract. It is obvious that a large
number of patients suffering from OA cannot function with anti-inflammatory therapy. Rather than avoiding NSAIDs or resorting to combination prophylactic therapies, the COX-2 specific inhibitors may solve the problem that has plagued the easy handling of this therapy, especially in older, high-risk patients.

The agents used for the treatment of OA can also be arbitrarily classified into at least two categories based on their time of onset of action: fast-acting, such as NSAIDs and corticosteroids, and slow-acting, having a few weeks delay of action. There are a number of such agents that, through clinical trials, have been shown effective at relieving the symptoms of the disease. Several of those agents are now in use for the symptomatic treatment of knee and hip OA and include diacerein, glucosamine sulphate, chondroitin sulphate (CS), and the avocado/soybean unsaponifiables. Their potential mode of action has been the subject of a number of in vitro and in vivo studies. These agents present several interesting properties including an extremely low incidence of side effects, a carryover effect of several weeks, with some having an additive effect with NSAIDs. These agents could provide an alternative for the symptomatic treatment of OA alone or in combination with an NSAID.

Among the local agents used for the symptomatic treatment of OA at the present time, the most popular are those given by intra-articular injection. Corticosteroids and hyaluronic acid (HA) are probably the most frequently used although their effectiveness, particularly over the long term, is still the subject of debate. A number of studies have been done and have demonstrated their usefulness and safety. Compared to HA, corticosteroids have a more rapid onset of action but their effect is much shorter. Their potential effect on disease progression is still hypothetical and is the subject of clinical evaluation.

The possibility of successfully inducing cartilage repair as a treatment for OA has been the dream of many scientists and physicians. It is a well-known fact that the repair capacity of cartilage is very limited, even more so during OA. There have been many approaches proposed including cell and tissue grafts and the use of synthetic matrices and biological agents, including growth factors. Interesting experimental results have been obtained. Although application in humans remain very limited at this time, the potential for the future is tremendous.

The development of noninvasive methods for observing the progression of OA has and would provide a very significant advance in this field of research. The development of new methods to measure biological markers to accurately and specifically estimate the degradative and/or the anabolic process in OA joints has been the subject of a large number of studies. These markers should ideally allow quantification of the metabolism of cartilage and other joint tissues such as the synovium and the subchondral bone to prognosticate and measure the response to treatment. Studies have already allowed identification of some molecules that may have some value as markers of disease progression. The usefulness of such markers is obvious and it is hoped that ongoing research will introduce more definite developments in this field. The primary use of molecular markers today is to facilitate the understanding of the disease process. Markers are used in epidemiological and genetic studies to clarify the OA processes and are used in clinical trials to strengthen efficacy arguments. Nonetheless, a goal for the clinical management of OA is to identify molecular markers that can be used for diagnosis and the monitoring of therapy. New tests measuring cartilage breakdown and other OA-related disease parameters are promising. A number of these tests, their