The Syndrome of Osteoarthritis

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ABSTRACT. The syndrome called osteoarthritis (OA) is characterized by change in structure and function of the joint. It is only symptomatic in about half of afflicted subjects. There is no diagnostic test. Progression is followed by a set of clinical variables that can be standardized for use in clinical trials. (*J Rheumatol 1997;24:766–7*)

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OSTEOARTHRITIS JOINT PAIN CLINICAL TRAILS

The syndrome we call osteoarthritis (OA) is characterized by alteration in the structure and function of the articulation or joint. These changes occur in the joint as a whole, including articular cartilage, underlying bone, and soft tissues. The pathophysiologic phenomena leading to the pathologic changes in the joint appear to result from biomechanical factors and activation of final common pathways of tissue damage. The etiology of OA is unknown in the majority of patients. However, there are a few conditions that appear related to OA, some etiologically. Typically, OA is defined as primary or idiopathic when there has been no identified associated known condition[1]. OA is defined as secondary when there is an identifiable related illness.

The pathology of OA is characterized by softening, fraying and loss of articular cartilage, osteophytes at the joint margins, and subchondral bony changes with formation of subchondral cysts and sclerosis. Although not as pronounced as with many inflammatory arthropathies, varying degrees of synovial inflammation are often present. Contractures result from involvement of the joint capsule and surrounding soft tissues. Deformity with malalignment of joints is common. Osteophytes may impinge on nerves or nerve roots about the spine.

SYMPTOMATIC OA

Even with our improved understanding of the pathologic process of OA, we have not established more than a crude correlation between the extent and degree of the anatomic changes and symptoms.

The most commonly quoted figure for the prevalence of OA is that roughly 20 million people in the United States have symptoms of OA[2]. This number is now dated and assuredly low. The effect of rheumatic diseases (mostly OA) is estimated to cost between 1 and 2.5% of the gross national product[3,4] or $8.6 billion 1983 US dollars[5].

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The prevalence of OA increases with age, increasing dramatically between ages 40 and 50. It is also more common in women. Examples of additional risk factors for OA include OA of the knee in obese women and combined cruciate/meniscal injuries. A subset of the former group may be at greater risk: Half of the obese women with a single OA knee may develop OA in the other knee within 2 years[6]. Identifying "at risk" populations may lend itself to trials on potential structure modifying drugs for OA.

The most common complaint of the patient with OA is pain. However, only about half of patients with radiographic OA have symptoms[7]. The reason(s) that half the patients with radiographic OA have or do not have pain is not always clear, since only some of the causes of pain have been researched[8]. In the future, studies oriented toward medications affecting pain may need to address specific causes of pain rather than the present concept of pain in general. It is appreciated that joint pain may lead to reduced function and disability, regardless of the presence of deformity, instability, or periarticular muscle weakness. There are now instruments that can grade the severity of pain, loss of function, and disability in OA.

CLINICAL TRIALS IN OA

Unfortunately, there is no "diagnostic test" for OA. OA involves a combination of clinical findings with radiographic and/or laboratory evidence[9–11]. Similarly, there is no validated method of monitoring progression of OA; however, imaging techniques are becoming more sophisticated and precise tools for evaluation, e.g., standardized radiographs, multifocal radiography, magnetic resonance imaging. Although not yet adequately developed, serum, synovial fluid, and urine are being studied for their potential as "molecular markers" for diagnosis and/or prognosis[12].

Clinical trials are now very specific about the recording of outcome measures. A carefully defined outcome variable in OA clinical trials needs to be selected on the basis of the therapeutic objective. As part of a workshop of the World Health Organization (WHO) and the American Academy for Orthopedic Surgeons, the methods to assess progression of OA of the hip and knee were reviewed[13]. In addition, the European Group for the Respect of Ethics and Excellence in Science completed their recommendations on methods for registration of drugs for OA[14].

To follow is the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group who are reviewing available clinical variables for measuring disease in OA. A workshop of the Osteoarthritis Research Society has combined recommendations of the above groups into a single task force report[15].

TYPES OF TRIALS

Concepts of medicinal therapy for OA are changing. A combined committee of the WHO and International League of the Associations for Rheumatology (ILAR) defined 2 classes of symptomatic therapy based on the onset and duration of the response to treatment[16]. They proposed a 3rd classification for agents that may alter the disease process. The 2 groups of symptomatic therapy may indeed represent the ends of a spectrum of one group, but the committee point out that not all symptomatic drugs are the same and probably should be studied using different trial designs. Selecting a trial design is dependent upon the proposed mechanism of action of the drug and the response expected.

Studies on drugs that are intended to reduce symptoms are termed symptom modifying drugs. Joint pain is usually measured in some specific manner and becomes the primary outcome variable. Medications used for symptom response have generally included analgesics and nonsteroidal antiinflammatory drugs (NSAID). More recent studies have explored intraarticular medications such as depo-corticosteroids and several forms of hyaluronic acid.

A drug may have effects on structure/function with no direct or indirect effect on symptoms. A drug in this class may either prevent the development of OA, or prevent / retard / reverse / stabilize the progression of established disease by altering the pathologic process(es) of OA. Benefit in the form of symptom relief or reduction may occur only after a prolonged period of administration. Alternatively, it is entirely possible that a drug that affects the pathology of OA may have no effect on joint symptoms. Hence, studies of drugs expected to modify the process of OA should measure outcome variables that reflect an alteration of joint structure. There is no ideal terminology, but drugs with this potential have been labeled "chondroprotective," and should perhaps be called structure modifying drugs for OA. To date, no agent has been proven to have structure modifying properties.

SUMMARY

It can be expected that the metrology and methodology of clinical trials of drugs for OA will change in the future, as they have in the recent past. The status of the measures to be used in the design of clinical trials on patients with OA available at present will require modification as new information becomes available. Investigators and regulatory and sponsoring agencies need to be aware of and support changes, particularly if they are research based. Investigators will need to adapt by including such information in their protocol design. Regulatory agencies will require flexibility to accept the newer technologies and methodologies. In this symposium we will address the core variables that need to be used in clinical trials of OA.

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