Use of animal models for testing drugs targeting osteoarthritis symptoms and articular tissue structural changes

J Martel-Pelletier*, JP Pelletier

Abstract

Introduction

Osteoarthritis (OA) remains a tremendous public health concern, in terms of both health-related quality of life and financial burden of disease. OA is a dynamic process involving at least three main tissues of the joint (cartilage, subchondral bone and synovial membrane) for which a global approach is now considered. OA management is based on a wide spectrum of therapeutic options to relieve pain and to try to delay progression of the disease. No disease-modifying OA drug (DMOAD) has yet been approved; consequently there remains a large unmet medical need for the treatment of OA.

A number of risk factors that can induce or accelerate the development of OA in the knee have been identified, including aging, genetic predisposition, high body mass index (BMI), joint injury, instability, malalignment, bone marrow lesions and meniscal lesion/extrusion. These factors can independently or in combination induce structural changes in the joint that are known to be characteristic of the disease. OA changes include the progressive degradation of articular cartilage characterised by fibrillation and erosion with the cloning of chondrocytes, the remodelling of the underlying subchondral bone with the appearance of bone marrow lesions including oedema and cysts, synovial inflammation characterised by hyperplasia of the synovial lining cells and fibrosis of this tissue, mononuclear cell infiltration of the sublining tissue and the growth of osteophytes at the margin of the joint representing an endochondral ossification process. The aim of this article was to discuss the use of animal models for testing drugs targeting osteoarthritis symptoms and articular tissue structural changes.

Short communication

Animal models capable of reproducing Osteoarthritis changes permit the study of Osteoarthritis structural alterations and pain in a time-wise fashion with sequential evaluation of the disease lesions and the possibility of being translational. A number of Osteoarthritis animal models have been developed and studied, using animals of different sizes, from small to large, some of which are spontaneous and others induced. Large animal models provide the advantages of anatomical and biomechanical similarities to humans, greater tissue sampling for exploring morphological changes and pathophysiological pathways, the capacity to use imaging and to investigate potential treatment targets, as well as being required by the regulatory agencies for pharmacokinetics and pharmaco-toxicological studies. For pain study, it is generally felt that naturally occurring models may be better than surgically induced models.

Conclusion

Experimental animal models of Osteoarthritis are of high interest as their use can help to provide insight into the disease process and evaluate therapeutic agents that may be effective in humans.

Introduction

Osteoarthritis (OA) is the most frequent musculoskeletal disorder to affect the majority of people in the second half of their lifespan. Osteoarthritis, which mainly affects the diarthrodial joints, is a chronic disease that develops progressively over decades, making it very difficult to precisely identify the different aetiological and risk factors that could influence its onset and development, as well as the pain associated with the disease. This article discusses how animal models provide practical and clinically relevant ways to study both the natural history and the response to treatment of knee Osteoarthritis.

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The authors have referenced some of their own studies in this short communication. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

OA animal models

Animal models provide practical and clinically relevant ways to study both the natural history of OA and the response to treatment. Developing animal models that more closely mimic human clinical conditions has become a priority in translational research and offers the significant advantage of exploring different
aspects of the morphological changes and pathophysiological pathways of the disease. A large number of OA animal models have been developed and studied, some of which are spontaneous and others induced. Spontaneous models refer to certain breeds of animals that are predisposed to OA and can develop symptoms at a relatively young age. The induced models are mostly those in which joint instability is induced by surgical or chemical techniques. Animals of different sizes are used, from small animals such as mice to larger animals such as dogs and horses. The choice of a particular animal model is multifactorial. Smaller animals are easier to use and less costly, but the information gathered may be less applicable to human OA. Larger animal models offer, among other advantages, a closer resemblance to human OA, particularly of the knee. The majority of these models have been the subject of several very comprehensive reviews, and in recent years, there have been significant efforts to standardise the outcome measures in OA animal model studies.

Animal models of OA pain

Pain is the most predominant clinical symptom of this disease. An unresolved issue in OA research is the lack of understanding of the mechanisms responsible for OA pain induction and maintenance. The most common treatments prescribed for OA are for symptomatic relief, to control the pain and improve joint function. Pain in OA is difficult to classify, as the factors contributing to its genesis such as inflammation and neuropathic and/or nociceptive pain components have yet to be fully identified. The specific sources of OA pain within the joint also remain elusive and are likely to be of multiple origins, including tissues of the joint such as the subchondral bone, the synovium and the soft tissues. Although a number of local and systemic treatments have been developed that can provide OA patients with some degree of relief, thus improving quality of life, there remains an urgent unmet need. Developing experimental animal models for OA pain assessment has been difficult. The relevance of most animal models of OA is mainly based on histopathologic similarities to the human disease. For pain study, animal models of naturally occurring OA may be more representative of the human disease than surgically induced models. Yet, it has been suggested that in view of the early involvement of meniscal damage in primary OA and the presence of nerve endings in the peripheral portion of the meniscus, the meniscus-based models may be relevant to the study of OA pain. Of note, in surgical models, it is acknowledged that the surgery itself could cause iatrogenic neuritis. It is therefore advised to compare results with sham surgery to control for such possible occurrences.

The development and use of rodent pain models have undoubtedly contributed to the understanding of the pathophysiology and pharmacology associated with acute and chronic pain states. For preclinical or proof of concept studies, small animals are generally chosen, and rat models have been used extensively. Although conditions involving joint instability (anterior cruciate ligament transection and/or meniscectomy) or articular degeneration (intra-articular injection of mono-iodoacetate; MIA) are used to evaluate analgesic compounds, the MIA model, while it does not produce the typical pathology observed in human OA, is often utilised. However, for translational pain research, the canine and feline privately owned naturally occurring models of OA offer some benefits. Indeed, in contrast with the smaller animals, these animals share both their living environment and way of life with humans, factors that may impact the pain level.

Testing for DMOAD

The ultimate goal for the treatment of OA has been to find agents that can reduce or stop the progression of the disease. Thus far no such treatment has been approved by the regulatory authorities as meeting the required guidelines. Moreover, there is, yet, no clear evidence of the superiority of one particular species over another for testing DMOAD effects. However, there is a general belief that larger animals provide the opportunity for a more global exploration of the effects of drugs on the different OA processes through clinical evaluation and quantification of OA structural changes by imaging and anatomical examination. The larger animal models also provide greater amounts of sample tissue, allowing for extensive exploration of the biochemical and molecular mechanisms of the disease and the effects of drugs. Importantly, testing in at least one large animal is an absolute requirement for pharmacokinetics and pharmacotoxicological studies according to the different regulatory agencies.

In the context of using animal models to study DMOADs, the timing of therapeutic intervention during the disease process may also be of importance. The questions remain as to whether experiments performed under therapeutic conditions are more meaningful than those from studies conducted under prophylactic conditions, as well as their importance when extrapolated to the clinical setting. However, studies using animal models have shown that compounds demonstrating DMOAD effects were most often found to be active under both conditions (prophylactic and therapeutic). Quite often, and this is particularly true with induced models, the experimental observation time is relatively short, a matter of a few weeks or months. Since the natural evolution of OA is chronic, it would seem logical and relevant that when OA animal model studies are planned for a drug development program, long-term confirmatory studies be included in the experimental planning. This is of particular importance as some
studies in which DMOAD effects have been shown in the early stages of the disease were found not to be predictive of the effects at a later stage.

Models in which noninvasive joint imaging such as magnetic resonance imaging (MRI) can be done over time and joint tissue structural changes reliably quantified, represent a significant advantage in following the disease process and the effects of DMOAD treatment, not only because the same animals can be followed at different periods but also for a longer duration. Such imaging technology has already been applied to investigate a variety of OA animal models including the dog, monkey, rabbit, guinea pig, rat and mouse. Importantly, with the interspecies variation occurring particularly in spontaneous animal models, a noninvasive monitoring of disease progression in animals could be highly advantageous. Although a high resolution of the MRI (or micro MRI) is required for small animal knees, for large animals, scanners used for humans are commonly employed, usually together with a coil designed for human knees or wrists and images read with systems adapted from those developed for human joints. Traditionally, the analysis of animal models of OA has been dependent on macroscopic/histological/histomorphological assessment of the articular tissues in which a large number of animals should be studied. The use of such imaging techniques could therefore lead to a dramatic reduction in animal usage, as recommended by the European Union and the United States.6,7

Treatment dosages and route of administration in animal models are also of importance, as they should aim to mimic clinical conditions. The therapeutic regimen should therefore target drug blood levels and exposure that are similar to those targeted in a human clinical setting. This is not always feasible, especially with smaller animals. However, this aspect with regard to the evaluation of a DMOAD is important for the validation of study results.

Age, size and gender as well as reproductive status of the animals also have important influences on study design and data. Furthermore, it is generally preferable to use skeletally mature animals to obtain data that are more applicable to humans, avoiding, for instance, the capacity to regenerate articular cartilage, as in the rabbit.8

OA animal model limitations
One must remember that OA animal models are for the most part driven by mechanical factors. In naturally occurring (idiopathic) OA, various aetiologic factors join forces to bring about the structural and molecular changes typical of the disease. Therefore, it is likely that some factors that contribute to the natural human disease may not be affected in certain animal models.

With regard to preclinical studies, the treatment benefits may be greater in animals because treatment is initiated at or close to the time of induced injury, in contrast to human clinical trials, in which DMOAD treatment is given (at least up to now) much later on in the disease process. Alternatives to address this would be longer study durations to allow for disease progression in the animal models, as for the most part preclinical animal studies have been of short duration or to take advantage of the animals that spontaneously develop OA.

The level of effectiveness of the treatment is rather difficult to compare between animal model and human studies due to the methodological differences. However, the discrepancies in findings between the medium and small animal models and the human disease could be due to the therapeutic agent being ineffective in humans, problems with dosing and/or the model may only reflect subsets of human OA.

The above issues are obviously representative of only a few to be dealt with when conducting DMOAD studies using animal models. Despite the limitations, a number of drugs or agents tested in different models have shown consistent DMOAD effects, and some have been positively translated into human clinical studies9-11. They demonstrate that DMOAD studies using animal models are useful in drug development programs. This, however, does not definitively answer the questions as to which model(s) would be preferential to use or the studies that need to be conducted and found conclusive before a drug can be qualified as a DMOAD.

Discussion
Animal models of OA have been used successfully for decades to explore the structural changes and pathophysiological pathways of OA. They allow the study of OA changes in a time-wise fashion and the sequential evaluation of the disease lesions. Although the use of animal models obviously presents limitations and is subject to criticism, translational animal research plays a critical role in helping to understand the disease process, improve methods of early detection and has also proven to be extremely valuable in identifying major therapeutic targets that have helped generate a number of major drug development programs in the field of OA.

Conclusion
Although the data from preclinical research cannot always be extrapolated to clinical trials, some drugs or agents studied in animal models have been found to have potential against pain and/or to alter the disease process in humans. As experience with these models evolves, along with our in-depth knowledge of their limitations, and the imaging techniques for animals improve, the use of such models in the development of

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For citation purposes: Martel-Pelletier J, Pelletier JP. Use of animal models for testing drugs targeting osteoarthritis symptoms and articular tissue structural changes. OA Musculoskeletal Medicine 2013 Nov 01;1(3):25.
DMOADs will become increasingly meaningful.

Competing interests
The authors are shareholders of ArthroLab Inc.

Conflict of interests
The authors are shareholders of ArthroLab Inc.

References