Osteoarthritis and Cartilage 22 (2014) 1639–1650

Osteoarthritis and Cartilage

Development and reliability of a multi-modality scoring system for evaluation of disease progression in pre-clinical models of osteoarthritis: celecoxib may possess disease-modifying properties

A. Panahifar †, J.L. Jaremko ‡ **, A.G. Tessier §, R.G. Lambert ‡, W.P. Maksymowych ||, B.G. Fallone § ¶ #, M.R. Doschak † †† *

† *Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada*
‡ *Department of Radiology & Diagnostic Imaging, University of Alberta, Edmonton, Alberta, Canada*
§ *Department of Medical Physics, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada*
|| *Department of Rheumatology, University of Alberta, Edmonton, Alberta, Canada*
¶ *Department of Oncology, University of Alberta, Edmonton, Alberta, Canada*
# *Department of Physics, University of Alberta, Edmonton, Alberta, Canada*
†† *Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada*

ARTICLE INFO

Article history:
Received 6 February 2014
Accepted 13 June 2014

Keywords:
Osteoarthritis
MRI
CT
Celecoxib
Glucosamine
Osteophytes

SUMMARY

Objective: We sought to develop a comprehensive scoring system for evaluation of pre-clinical models of osteoarthritis (OA) progression, and use this to evaluate two different classes of drugs for management of OA.

Methods: Post-traumatic OA (PTOA) was surgically induced in skeletally mature rats. Rats were randomly divided in three groups receiving either glucosamine (high dose of 192 mg/kg) or celecoxib (clinical dose) or no treatment. Disease progression was monitored utilizing micro-magnetic resonance imaging (MRI), micro-computed tomography (CT) and histology. Pertinent features such as osteophytes, subchondral sclerosis, joint effusion, bone marrow lesion (BML), cysts, loose bodies and cartilage abnormalities were included in designing a sensitive multi-modality based scoring system, termed the rat arthritis knee scoring system (RAKSS).

Results: Overall, an inter-observer correlation coefficient (ICC) of greater than 0.750 was achieved for each scored feature. None of the treatments prevented cartilage loss, synovitis, joint effusion, or sclerosis. However, celecoxib significantly reduced osteophyte development compared to placebo. Although signs of inflammation such as synovitis and joint effusion were readily identified at 4 weeks post-operation, we did not detect any BML.

Conclusion: We report the development of a sensitive and reliable multi-modality scoring system, the RAKSS, for evaluation of OA severity in pre-clinical animal models. Using this scoring system, we found that celecoxib prevented enlargement of osteophytes in this animal model of PTOA, and thus it may be useful in preventing OA progression. However, it did not show any chondroprotective effect using the recommended dose. In contrast, high dose glucosamine had no measurable effects.

Introduction

Osteoarthritis (OA) is classically characterized by cartilage degeneration, and abnormal bone adaptations such as formation of permanent osteophytes and subchondral bone sclerosis. Despite a number of available palliative treatments, there is currently no disease-modifying treatment. Having a safe pharmacodynamic profile, glucosamine, an amino monosaccharide used in biosynthesis of glycosaminoglycans in articular cartilage, alone or in combination with chondroitin sulfate has been used worldwide for

* Corresponding author. Faculty of Pharmacy & Pharmaceutical Science, 2020J Katz Group-Rexall Centre for Pharmacy & Health Research, University of Alberta, Edmonton, Alberta T6G 2N8, Canada. Tel: 1-780-492-8758.
** Corresponding author. Department of Radiology & Diagnostic Imaging 2A2.41 WMC, University of Alberta Hospital 8440 112 Avenue NW Edmonton, Alberta T6G 2B7, Canada, Tel: 1-780-407-6907.
E-mail addresses: a.panahifar@ualberta.ca (A. Panahifar), jjaremko@ualberta.ca, jjaremko@ualberta.ca (J.L. Jaremko), Anthony.tessier@albertahealthservices.ca (A.G. Tessier), rlambert@ualberta.ca (R.G. Lambert), walter.maksymowych@ualberta.ca (W.P. Maksymowych), bfallone@ualberta.ca (B.G. Fallone), mdoschak@ualberta.ca (M.R. Doschak).

http://dx.doi.org/10.1016/j.joca.2014.06.013
1063-4584/

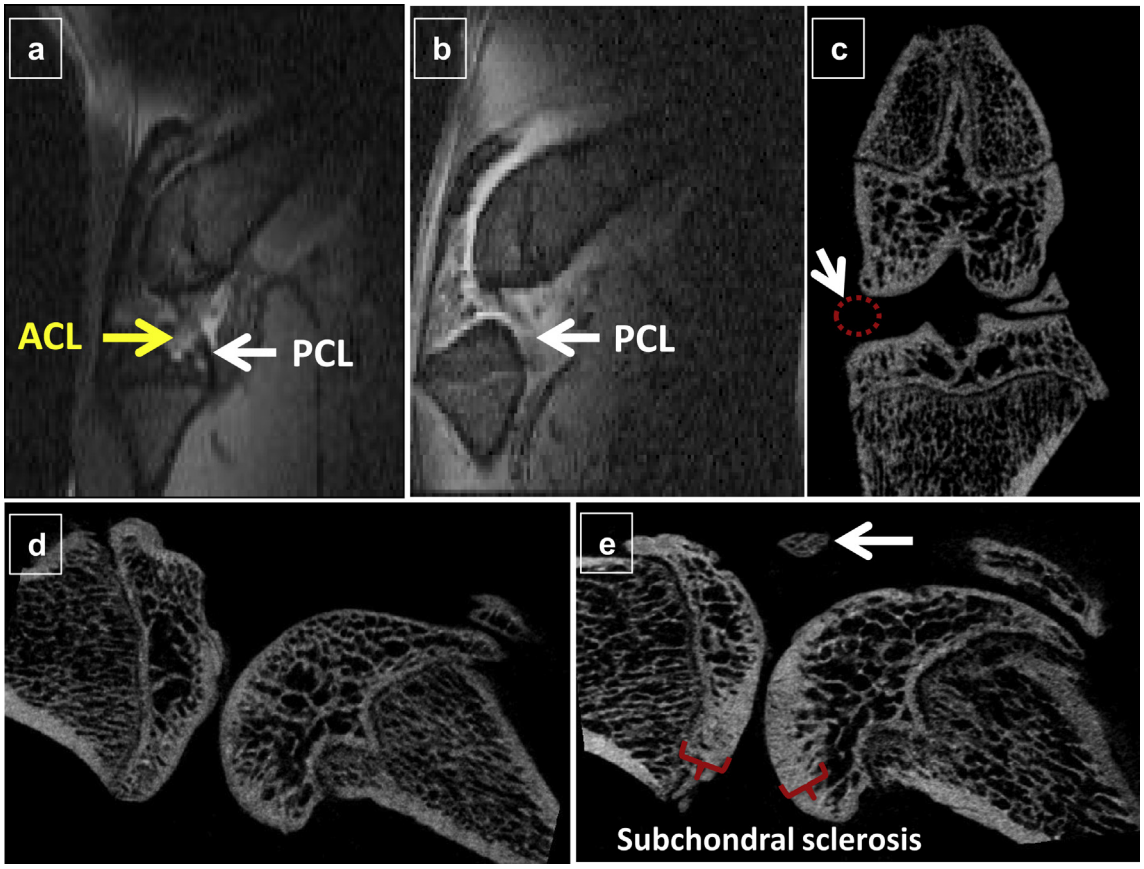

Fig. 1. a) Sagittal T1-weighted/fat suppressed MRI prior to surgery, displaying intact ACL and PCL; b) Sagittal image of the same joint after 12 weeks showing only PCL after transection of ACL (Gd-enhanced); c) coronal micro-CT from the same rat showing absence of medial meniscus (arrow and circle) at 1 day post-surgery. Note that unlike in humans, menisci are ossified in rats. d, e) Sagittal micro-CT of the same joint at baseline (d) and 12 weeks post-surgery (e). Note subchondral sclerosis in femur and tibia (brackets). Also, presence of a mineralized loose body (arrow) that was absent at baseline is notable.

management of OA symptoms, albeit without consensus regarding its disease-modifying capacity[1,2]. Differences in formulation and bioavailability, stage of the disease[2] in experimental groups, and different administered doses[3] have been suggested as factors responsible for the controversy. Furthermore, performing studies in different experimental models as well as variability in outcome measures used makes direct comparisons among these studies challenging.

In the current study we aimed to evaluate the effect of glucosamine and another agent thought to have disease-modifying properties, celecoxib, head-to-head in an established animal model of post-traumatic OA (PTOA). As a prerequisite, it is vitally important to measure the effects of experimented therapeutics using standardized and validated methods for outcome assessment. Several scoring systems exist based on a single modality for use in humans such as the traditional and widely used radiological Kellgren–Lawrence[4] system or newer magnetic resonance imaging (MRI)-based systems like WORMS [5] or BLOKS[6]. However, due to the complex nature of the disease, the measuring system must be not only sufficiently discriminatory to detect minor and early changes, but also assess multiple outcome domains relevant to the clinical and pathophysiological aspects of disease. There are some features that either cannot be detected with one modality or the sensitivity would be low. For instance, we have observed that osteophytes are detectable by computed tomography (CT) long before they appear on MRI or planar X-ray, owing to higher resolution and greater bone/soft tissue contrast of CT (observation from a pilot study, data not shown). Therefore, in the current report we have focused effort towards incorporating as many outcomes as possible to design a comprehensive scoring system.

In this manuscript we describe a comprehensive multimodal approach to the assessment of experimental OA. Bony adaptations such as osteophyte formation, subchondral sclerosis, and the occasional presence of calcified loose bodies were scored mainly by the use of micro-CT. Soft tissue abnormalities including synovitis, joint effusion, cysts, loose bodies and edema were identified and scored using micro-MRI. Cartilage structure at different time points was assessed by histology, as the most sensitive tool for the purpose.

Since animal studies are a prerequisite to human trials, our objective was to develop a multi-modality scoring system combining MRI, CT and histology features applicable to rats as the most available and extensively studied experimental model of OA. However, this system can be easily optimized for use in other animal models. Using this system, we sought to determine whether two controversial therapies, celecoxib and glucosamine, were actually disease-modifying agents in a pre-clinical rat model of PTOA.

Methods and materials

Surgical model of PTOA

PTOA was surgically induced in 27 skeletally mature (9-month-old) Sprague–Dawley rats (Charles River Laboratories, US) by Knee Triad Injury (KTI) surgery[7], with an additional three rats included as