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Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis

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Summary

Background: Recent innovations in the pharmaceutical drug discovery environment have generated new chemical entities with the potential to become disease modifying drugs for osteoarthritis (DMOAD's). Regulatory agencies acknowledge that such compounds may be granted a DMOAD indication, providing they demonstrate that they can slow down disease progression; progression would be calibrated by a surrogate for structural change, by measuring joint space narrowing (JSN) on plain X-rays with the caveat that this delayed JSN translate into a clinical benefit for the patient. Recently, new technology has been developed to detect a structural change of the OA joint earlier than conventional X-rays.

Objective: The Group for the Respect of Ethics and Excellence in Science (GREES) organized a working party to assess whether these new technologies may be used as surrogates to plain x-rays for assessment of DMOADs.

Methods: GREES includes academic scientists, members of regulatory authorities and representatives from the pharmaceutical industry. After an extensive search of the international literature, from 1980 to 2002, two experts meetings were organized to prepare a resource document for regulatory authorities. This document includes recommendations for a possible update of guidelines for the registration of new chemical entities in osteoarthritis.

Results: Magnetic resonance imaging (MRI) is now used to measure parameters of cartilage morphology and integrity in OA patients. While some data are encouraging, correlation between short-term changes in cartilage structure observed with MRI and long-term radiographic or

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clinical changes are needed. Hence, the GREES suggests that MRI maybe used as an outcome in phase II studies, but that further data is needed before accepting MRI as a primary end-point in phase III clinical trials. Biochemical markers of bone and cartilage remodelling are being tested to predict OA and measure disease progression. Recently published data are promising but validation as surrogate end-points for OA disease progression requires additional study. The GREES suggests that biochemical markers remain limited to 'proof of concept' studies or as secondary end-points in phase II and III clinical trials. However, the GREES emphasizes the importance of acquiring additional information on biochemical markers in order to help better understand the mode of action of drugs to be used in OA. Regulatory agencies consider that evidence of improvement in clinical outcomes is critical for approval of DMOAD. Time to total joint replacement surgery is probably the most relevant clinical end-point for the evaluation of efficacy of a DMOAD. However, at this time, time to surgery can not be used in clinical trials because of bias by non disease-related factors like patient willingness for surgery or economic factors. At this stage, it appears that DMOAD should demonstrate a significant difference compared to placebo. Benefit should be measured by 3 co-primary end-points: JSN, pain and function. Secondary end-points should include the percentage of patients who are 'responder' (or 'failure'). The definition of a 'failure' patient would be someone with progression of JSN>0.5 mm over a period of 2–3 years or who has a significant worsening in pain and/or function, based on validated cut-off values. The definition of the clinically relevant cut-off points for pain and function must be based on data evaluating the natural history of the disease (epidemiological cohorts or placebo groups from long-term studies). These cut-offs points should reflect a high propensity, for an individual patient, to later require joint replacement.

Conclusion: GREES has outlined a set of guidelines for the development of a DMOAD for OA. Although these guidelines are subject to change as new information becomes available, the information above is based on the present knowledge in the field with the addition of expert opinion.

Key words: Drugs, Osteoarthritis, Registration, Treatment, Studies, Biochemical markers.

Introduction:

Due to the rapidly increasing fraction of aging people in the World population, osteoarthritis (OA) is becoming a more significant public health problem. Most people over age 60 will have some form of OA and about half will have symptoms[1,2]. Even though significant progresses have been made to provide short term relief of pain from OA, the major unmet need for OA is pharmacological agents able to stop or reverse the progression of structural damage. Recent innovations in the pharmaceutical drug discovery environment have generated new chemical entities (NCE's) with the potential to become disease modifying osteoarthritis drugs (DMOAD's). Appropriate clinical trials will have to be designed to demonstrate the favorable benefit/risk ratio of any new compound prior to approval from a regulatory agency for labeling as a DMOAD's.

However, the major difficulty for potential DMOAD's clinical development will be to meet the current regulatory requirements. Both European and US regulatory guidelines[3–5] specify that in order to gain a DMOAD indication, clinical studies need to demonstrate that a new NCE can slow down diseases structural progression as measured by joint space narrowing (JSN) on plain X-rays and that this delayed JSN translates into a clinical benefit for the patients.

One of the limitations of JSN measurements is related to the very small changes observed over time and to the high precision error of the measurement. More recently, MRI has been tested for measuring cartilage morphology and integrity in OA patients[6]. Even though some data are encouraging, their interpretation is still controversial. Measurements of biochemical markers of cartilage turnover have also been used in an attempt to predict OA and measure disease progression. Their future use looks promising but their validation as surrogate endpoint for OA disease progression will require significant additional work[7].

In this context it appears that a very relevant clinical endpoint to evaluate the efficacy of DMOAD's in clinical trials would be the need for total joint replacement (TJR). This would be analyzed using a time to event statistical method. However and even though guidelines with specific criteria for TJR are available in many countries, this endpoint has not been widely used so far in clinical trials. This is consequent to the fact that the evaluation of the actual time to the need for TJR is most often confounded by non-disease related factors like patient willingness for surgery or local economic factors and health policies. Hence, unlike other disease areas like osteoporosis where fracture occurrence is used as a critical event for time to event analysis, evaluation of efficacy of DMOAD's relies on longitudinal measurements of continuous variables.

The objective of this paper is to try to overcome these existing difficulties in proposing a set of criteria which could be used as surrogates for the time to surgery for TJR.

Method

The Group for the Respect of Ethics and Excellence in Science (GREES) 'Section Osteoarthritis', met in two separate occasions in January and September 2003. The GREES includes academic scientists with an extensive background in the considered field (i.e. rheumatology, public health, radiology, biochemistry, epidemiology and health economics) members of national regulatory authorities and representatives of the pharmaceutical industry. We carried on an extensive search of the electronic databases (Medline and Premedline, Biasis Preview Healthstar, Cochrane Library of Randomized Controlled Trials, Cochrane Database of Systematic Reviews, Current Contents and EBM Reviews) from 1980 until 2002. Generic keywords related to the thesaurus of each database were used. Since not all data are indexed in the electronic databases, we conducted a hand search (O.B.) of the reference section of each of the articles retrieved by the primary search until no new paper was found. We also contacted GREES members (scientists or industrial partners) active in osteoarthritis. The invited experts made a critical analysis of the available science. The objective is to provide European regulatory authorities with a working document allowing to update, if needed, the guidelines for registration of drugs in osteoarthritis.

Results

CURRENT REGULATORY GUIDELINES

Regulatory guidelines for the approval of drugs to be used as DMOADs for the treatment of OA were published or updated recently in the US and in Europe[3,4].

The US FDA guidelines specify that because it is widely (but not universally) accepted, JSN improvement of hip and knee implies cartilage preservation and will thus be reflected in clinical benefit[3]. However they also state that determining what change in JSN of the knee or hip is clinically relevant to the patient with OA is fundamental, but currently unknown. Hence the FDA guidelines strongly suggest that measurements of clinical outcomes should be collected in all trials regardless of expectations on JSN, because their assessment is critical for the analysis of the overall risks and benefits of the product.

In a very similar way the European CPMP guidelines[4] clearly recommend the use of plain X-ray for JSN measurements as a primary endpoint even though it is recognized that the nature and magnitude of structural changes that are likely to be clinically relevant in the long term remain uncertain. Therefore it is requested by the regulatory authorities[3,4] that clinical endpoints such as pain, disability or time to the need for total joint replacement (TJR) surgery should also be assessed during clinical studies.

Overall, both US and European guidelines require improvement of clinical outcomes to correlate to delay in JSN progression for DMOAD approval. In other words, as long as it is correlated to an improvement of clinical outcomes, a delay in JSN progression is considered as an appropriate primary endpoint and as a surrogate endpoint for total joint replacement which is the critical event characteristic of a medical treatment failure for OA It is assumed that a delay in JSN will consequently delay the need for total joint surgery, and can hence be interpreted as a treatment success for DMOAD's.

OUTCOMES OF RECENT CLINICAL TRIALS WITH DMOAD'S

Only a limited number of potential DMOAD's have shown a delay in JSN associated with improvements of clinical symptoms[8–11]. These publications report the results obtained after treatment of hip or knee OA patients with diacerein and glucosamine[10,11].

Diacerein, an interleukin-1 inhibitor, was shown to reduce pain and functional impairment in patients with hip or knee OA[9]. The ECHODIAH study[10] evaluated the effect of diacerein on the progression of JSN in patients with hip OA over 3 years of therapy. The primary endpoint of the study was the radiographic progression of OA measured at the hip, and expressed as the proportion of patients with radiographic JSN of at least 0.5 mm during the study period. Even though diacerein had no effect on OA symptoms in this study, the percentage of patients with radiographic progression was significantly lower in patients receiving diacerein than in patients receiving placebo. In addition the study also showed that there was a non statistically significant trend towards fewer decisions of total hip replacement procedures in the diacerein group as compared to the placebo group.

Clinical studies evaluating the effect of 3 years of glucosamine sulfate administration to patients with knee OA also provided evidence that this compound could significantly reduce JSN at the medial compartment of the knee as compared to placebo[11–13]. In these same studies a slight worsening in symptoms was evident at the end of the treatment with placebo, compared to the improvement observed after glucosamine sulfate.

Overall these clinical studies evaluating the effect of diacerein and glucosamine on OA disease progression have shown the feasibility of detecting a structure modifying effect using plain X-ray JSN measurements. However long term studies will need to confirm that administration of these pharmacological agents leading to a delay in progression of JSN could also deliver clinical beneficial effects to the OA patients.

AVAILABLE TECHNOLOGIES TO MEASURE OA DISEASE PROGRESSION

The outcome of the studies reported above underlines that there is still limited understanding on how OA clinical expression patterns are linked to longitudinal structural changes in cartilage. Plain X-rays, MRI and biochemical markers have been used to measure OA disease progression over time. Each one of these technologies carries limitations.

The limitation of conventional radiography for cartilage assessment is that it only permits an approximation of cartilage thickness change with measurement of JSN. Even though radiographic measures of joint space width (JSW) changes has been recommended as primary measure of efficacy for DMOAD's, precision of this measurement is quite variable and dependent on standardized radiographic techniques. Small positional changes from one measurement to the other can jeopardize reproducibility of JSW measurements. The degree of flexion of the knee determines the regions of cartilage taken into account for the measurements. Several methods including fluoroscopy, foot maps and positioning devices can be used to obtain satisfactory measurements, but despite standardization of radiographic techniques the rates of JSN can still vary widely[14,15] and lead to significant difficulties in the management of large sample size longitudinal clinical trials. In addition, hip and knee X-rays only provide limited information on the status of articular and peri-articular soft tissues which may play a significant role in OA progression and clinical expression. Recent studies have also shown that alterations in the condition of the menisci[16] could cause radiographic JSN independently of cartilage thinning.

Measurements of JSW at the hip seems less variable and more reproducible when using computer assisted methods[17,18].

Magnetic resonance imaging (MRI) has been seen recently as having potential for evaluation of joints in OA due to its ability to evaluate morphology and integrity of the articular cartilage. It also provides a direct image of the soft tissues around the joint.

Significant efforts and studies have been dedicated to use MRI as a method of quantification of cartilage volume and thickness. For technical reasons the outcome of these studies has not been not very satisfactory for the hip cartilage assessment. For the knee, several studies have shown longitudinal cartilage volume losses in the range of 3 to 7% per year in OA patients[19–22]. However, other studies have not detected any changes in cartilage volume in patients with knee OA over a 3 years time period[23]. More concerning is the fact that no strong correlations have been shown between loss of cartilage volume measured by MRI over time and changes in X-ray JSN or in clinical symptoms. Hence, larger longitudinal studies are still needed to clarify the clinical relevance of MRI measured cartilage volume in OA disease progression.

Exploration of changes in the non cartilage components of the OA joint (e.g. synovium and effusions, bone marrow 'edema') is also ongoing with MRI and may offer opportunities for the discovery new parameters of interest[24].

However the most promising MRI capabilities could well be the one developed to directly evaluate the changes in cartilage matrix components (e.g. collagen and glycosaminoglycan). These approaches could be of high interest to detect early changes in cartilage components in response to pharmacological intervention

- several studies have shown that MRI T2 relaxation can be used as a qualitative assessment of collagen in the cartilage matrix[25,26].
- one of the main constituents of cartilage which is lost in early OA, and which one would like to replace as part of therapeutic interventions, is the glycosaminoglycan (GAG) component. A new technique known as dGEMRIC (delayed Gadolinium Enhanced MRI of Cartilage) is being developed to directly image the GAG component in cartilage[27–29].
- another approach under investigation is sodium MRI. The rationale of this approach is driven by the fact that early stage of OA is primarily associated with a loss of proteoglycan (PG) and minimal changes in collagen. PG carries a negative fixed charge density due to its sulfate and carboxyl groups and thereby attracts sodium ions to maintain neutrality. Consequently, sodium concentration can be used as an indirect measurement of PG content. Therefore sodium MRI of the knee has the potential for detecting early degenerative changes in cartilage[30].

The joint is a complex structure involving cartilage, synovial tissue and bone. Alterations and destruction of these components during progression of OA will release fragments or biological markers specific of these tissues in synovial fluids, blood and urine[31,32]. There has been progress into the use of some of these markers for the prediction or measurement of progression of OA, as well as for the evaluation of response to pharmacological intervention with compounds of potential DMOAD activity[33,34]. The potential for reliable and responsive markers is large. However, further work is still needed on how changes measured in some of these biochemical markers of cartilage turnover correlate with OA disease progression.

Discussion

Overall none of the multiple options available to measure changes in cartilage structure and integrity over time has given full satisfaction to assess OA disease progression. Even though most of the measurement methods can detect changes related to the impact of OA on cartilage and other peri-articular tissues, these changes have not been clearly correlated so far with beneficial outcomes for the patient. However measurement of JSN using plain X-ray is the most documented method to date, and this supports its use as the method of reference for DMOAD's efficacy evaluation in phase III clinical trials. At this stage it seems that the use of MRI or biochemical markers measurements has to remain limited to early phases proof of concept, dose ranging studies or as secondary endpoint in phase III clinical studies.

Tools for clinical evaluation of symptom-modifying drugs in OA have also been proposed but they are not appropriate for evaluation of DMOAD therapy[35].

Subsequently, the most relevant endpoint for DMOAD phase III studies still appears to be the decision of performing a TJR procedure. The use of TJR as an event characterizing treatment failure – in the same way as occurrence of fractures is used for the clinical evaluation of antiosteoporotic drugs – would provide the most robust and clinically relevant endpoint to assess the efficacy of a DMOAD.

Several attempts have been made to try to standardize the need for hip and knee total joint replacement across multiple countries. However these efforts are mostly dedicated to better allocation of resources in daily patients care and will not address specifically the need of validating an endpoint which could be used in clinical trials assessing the effect of pharmacological intervention on OA disease progression.

Patterns of clinical expression and disease progression are also different at the hip and at the knee and this justifies the need for specific subset of criteria for the two locations.

The use of the occurrence of TJR as a primary endpoint in clinical trials faces two major difficulties:

- OA is a slow progressing disease in most of the cases, and in the absence of a validated marker to identify patients at risk of fast progression, the use of TJR as an outcome measurement would raise a significant feasibility hurdle as it would lead to study design with several years of treatment duration and large patients sample sizes.
- the decision leading to a TJR procedure is not only driven by criteria of OA severity at this same joint, but is confounded by the patient willingness for surgery and in many cases by the intervention of third party payers driven by local public health policies.

Hence the identification and validation of a set of surrogate criteria which could provide evidence of a slower progression of the disease in patients treated with a NCE as compared to placebo would prove to be much useful for clinical investigation and evaluation of DMOAD's.

The selection of appropriate surrogate criteria for the need to surgery must take into account the following considerations:

- differentiation of clinical criteria from non disease related factors
- sensitivity to change
- relative evolution and characteristics of hip OA compared to knee OA
- relation between imaging changes and pain and functional capabilities

The correlation between X-ray changes and clinical outcomes (pain, function) is stronger at the hip than at the knee.

The need for surgery is the consequence of a conservative therapy failure. Hence in studies aiming at the identification of structure modifying properties, patients with very symptomatic OA and advanced radiological lesions should not be considered for clinical trials. Patients with mild to moderate OA lesions will be included in these trials. A treatment failure can be defined as a patient reaching a threshold of severity (clinical or radiological) or showing an aggravation from baseline under therapy. For an individual patient the time from baseline up to this threshold of severity can be considered as a theoretical time to surgery. This approach would allow to design clinical studies using a time to event analysis.

At this stage it appears that DMOAD's should demonstrate a significant difference compared to placebo or an active control in terms of JSN, pain and function over time

(three co-primary endpoints). Furthermore, as secondary end-points, the percentage of 'responders' (or 'failures') should be assessed. The definition of treatment 'failure' for a patient would be either a JSN >0.5 mm over a 2–3 years period or a significant worsening in pain and/or function based on validated cut-off values. The definition of the clinically relevant cut-off points for pain and function must be based on the natural history of the disease. These cut-off points should reflect a high propensity for an individual patient to later require joint replacement.

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