Osteoarthritis and Cartilage xxx (2015) 1–8

Osteoarthritis and Cartilage

Review

Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement

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ARTICLE INFO

Article history:
Received 5 January 2015
Accepted 7 July 2015

Keywords:
Osteoarthritis
Registration of drugs
Guideline

SUMMARY

Objective: The European Society on Clinical and Economic aspects of Osteoporosis and Osteoarthritis (ESCEO) organised a working group to evaluate the need for updating the current European guideline on clinical investigation of drugs used in the treatment of osteoarthritis (OA).
Design: Areas of potential attention were identified and the need for modifications, update or clarification was examined. Proposals were then developed based on literature reviews and through a consensus process.
Results: It was agreed that the current guideline overall still reflects the current knowledge in OA, although two possible modifications were identified. The first relates to the number and timing of measurements required as primary endpoints during clinical trials of symptom-relieving drugs, either drugs with rapid onset of action or slow acting drugs. The suggested modifications are intended to take into consideration the time related clinical need and expected time response to these drugs – i.e., a more early effect for the first category in addition to the maintenance of effect, a more continuous benefit over the long-term for the latter – in the timing of assessments.
Secondly, values above which a benefit over placebo should be considered clinically relevant were considered. Based on literature reviews, the most consensual values were determined for primary endpoints of both symptom-relieving drugs (i.e., pain intensity on a visual analogue scale (VAS)) and disease-modifying drugs (i.e., radiographic joint-space narrowing).

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http://dx.doi.org/10.1016/j.joca.2015.07.001

Conclusions: This working document might be considered by the European regulatory authorities in a future update of the guideline for the registration of drugs in OA.

Introduction

Osteoarthritis (OA) is a common, slowly progressive condition that may affect all joint structures, and is a major cause of pain and chronic disability in the elderly[1]. Current treatment includes non-pharmacological and pharmacological therapies that are taken into account in a recent algorithm developed to advise on the possible stepwise approach to the sequence of interventions[2].

Symptomatic drugs are usually divided into drugs with a rapid onset of action such as paracetamol or other analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) – (being either non-selective or selective COX-2 inhibitors) – or intra-articular injections of corticosteroids, and Symptomatic Slow Acting Drugs for OA (SYSADOAs) such as glucosamine and chondroitin sulfate or intraarticular hyaluronic acid. Drugs with potential beneficial effect on the joint structure (Disease Modifying OsteoArthritis Drugs, DMOADs) may be developed in the future: these may or may not have a direct effect on symptoms and they may delay the disease process, as preliminarily suggested by currently available SYSADOAs showing some hints of modification of joint structure[3,4,5].

A first European regulatory document aimed at providing advice for the development of drugs in OA was issued in 1998[6]. The latest version of the Committee for Medicinal Products for Human Use (CHMP)/European Medicines Agency (EMA) guidance[7], adopted in 2010, is a revision of that document.

The first version of the guideline[6] was derived from a report by the Group for Respect of Ethics and Excellence in Sciences (GREES)[8]. This group has been thereafter providing recommendations for an update based on a critical analysis of the available science[9–11].

A substantial part of these proposals were taken into account in the 2010 current version of the CHMP/EMA guidance[7].

Several elements of the guideline are the subject of much debate. They are mainly related to the cut-off values that should define a clinically relevant symptomatic or structural improvement and to the timing of assessments that should be collected throughout confirmatory clinical trials.

For this reason, under the auspices of the European Society on Clinical and Economic aspects of Osteoporosis and Osteoarthritis (ESCEO), a special section of the GREES was convened in May 2014 to discuss these issues in the light of recent data and expert opinion. The consensus view, which might be possibly considered in future guidelines, is presented in this discussion paper.

Methods

As in previous initiatives and publications, the GREES/ESCEO working group consisted of clinical scientists expert in the field of OA in academia and consulting for drug development within the pharmaceutical industry, and representatives of national or European licensing authorities giving their contribution on a personal basis.

As a general methodology, the group reviewed the current version of the CHMP/EMA guideline in detail[7].

The members of the working group were asked to assess the possible need for revision of the guideline in view of their knowledge of the field and of the clinical literature, in order to identify the areas of potential attention. The group judged that there was no need to revise any of the first four sections within the CHMP/EMA document (including disease definition, drug categories and patient selection). Conversely, there was general consensus that specific parts within the methods for assessing efficacy section (Section 5) for both symptom modifying and structure modifying drugs, with particular respect to the clinical relevance of the changes on the primary endpoint(s) and the timing of assessment, may be in need of clarification. This would inevitably affect also the section on the design of the studies (Section 6.2) with particular regard to confirmatory trials, while the guideline sections on 'early studies in man' (Section 6.1) or the 'clinical safety evaluation' (Section 7) were not explicitly covered by the discussion.

Members of the group (SR, OB and GH-B) were therefore asked to prepare a full review of the literature on these topics and to present the results at the May 2014 meeting. After the presentations, a comprehensive discussion was hold within the group and shared conclusions were reached.

Results

Table I summarizes the proposed changes to the current guideline document, as extensively reported below.

Primary endpoint and design of clinical studies of symptom modifying drugs

Symptom modifying drugs act on pain and potentially on functional disability. According to the CHMP guideline, Phase III pivotal studies should have a randomised, double-blind, parallel group design. A three-arm study with placebo and a most appropriate active comparator is recommended for symptom modifying drugs: the nature of the active comparator can be discussed between the regulatory authority and the sponsor e.g., in a scientific advice procedure. Long-term efficacy data (e.g., on an open label extension) as well as data after stopping therapy should be provided. Importantly, the absence of deleterious effects on joint structure should be established from imaging (e.g., radiographic) data obtained over at least one year.

The recommended primary endpoint for clinical development of symptom modifying drugs is pain attributable to the target joint. Pain referring to a recent period, ideally the past 24 or 48 h, should be self-assessed by the patient using a validated method (e.g., the visual analogue scale-VAS, Likert scale…). Validated multidimensional tools with pain subscale index are also acceptable. Functional disability may be considered as an important co-primary endpoint, again with validated disease-specific and joint-specific instruments. However, if functional disability is not a co-primary endpoint and benefit is only shown for pain, at least the absence of deterioration of physical function should be demonstrated.

In the opinion of the working group, some specific clarifications and recommendations were considered necessary and are given below for the development of drugs with rapid onset of actions and SYSADOAs, respectively.

Symptom modifying drugs with rapid onset of action

The current guideline recommends that the primary endpoint, i.e., the change from baseline in pain intensity and optionally

Please cite this article in press as: Reginster J-Y, et al., Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement, Osteoarthritis and Cartilage (2015), http://dx.doi.org/10.1016/j.joca.2015.07.001