EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2015
EMA/CHMP/80184/2015
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis

Agreed by Rheumatology Immunology Working Party	February 2015
Adopted by CHMP for release for consultation	26 February 2015
Start of public consultation	1 April 2015
End of consultation (deadline for comments)	30 June 2015

Comments should be provided using this template. The completed comments form should be sent to RIWPsecretariat@ema.europa.eu

Keywords	axial spondyloarthritis, ankylosing spondylitis, ASAS criteria, Guidance

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1. Introduction

Classification and epidemiology

The concept of spondyloarthritis (SpA) includes ankylosing spondylitis (AS), psoriatic arthritis, arthritis/spondylitis with inflammatory bowel disease, reactive arthritis, as well as undifferentiated SpA. All of these can present with a predominantly peripheral or axial subtype. In 2009 ASAS (Assessment in SpondyloArthritis International Society) suggested criteria defining the entity of axial spondyloarthritis (axial SpA) including a broader set of patients by focusing on MRI findings and HLA-B27 (1,2). This entity includes patients with sacroiliac joint changes on x-ray (i.e. fulfilling the 1984 New York AS criteria) as well as those with similar symptoms but without radiological findings ("non-radiological axial spondyloarthritis, nr-AxSpa"). The prevalence for AS has been estimated to be between 0.1% - 0.2% of the population and the incidence rate to 6/100.000/year in Western Europe. AS is more common in males (male to female ratio is estimated to be 2-3:1).

Clinical features and course of disease.

AS is a chronic inflammatory disease that involves primarily the sacroiliac joints and the axial skeleton. Further, the entheses, peripheral joints and extra-articular organ sites such as the anterior uvea maybe involved. Clinical manifestations usually begin in late adolescence or early adulthood and onset after age 45 is rare. Classical symptoms include lower back pain with predominant nocturnal pain and morning stiffness. Although AS may have a waxing and waning course it is a chronic disease that over time may cause substantial pain and disability. Functional limitations in the early phases of disease relate to inflammation but may increase with persistent disease resulting in new bone formation. Patients with nr-axSpA can present with disease features and a level of disease activity similar to those observed in patients with AS.

Prognostic factors

There are no solid prognostic parameters besides early radiographic progression, but male sex, smoking, early age of onset, increased CRP, and hip involvement early in the disease course are associated with poor prognosis.

Drug treatment

Non-steroidal anti-inflammatory drugs (NSAIDs) have shown documented effect to control pain with acceptable safety in short term studies and form the basis of drug treatment (3). Whether the long term use of NSAIDs provides beneficial or deleterious effects on the radiographic progression of the disease is still under debate. Intra-articular corticosteroids may be used for sacroiliac or peripheral joint inflammation whereas systemic corticosteroids in general are of little benefit. There is some evidence for beneficial effects of sulfasalazine in AS patients with peripheral arthritis (4). Support for the use of MTX in AS is lacking (5). Several TNF-inhibitors (TNFi) are established as second line treatment option of AS (6). In recent several years studies of treatment with TNFi in AS , defined according to the modified New York criteria have been published. In 2012 the first TNFi was approved for the treatment of axial SpA, without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein and / or magnetic resonance imaging, in adult patients who have had an inadequate response to, or are intolerant to NSAIDs.

2. Problem statement

The ASAS criteria for axial SpA, the approval of TNFis for the treatment of AS as well as for nr-axSpA and the use of more elaborated outcome measures for the treatment (eg. AS disease activity score, AS 20/40 etc.) indicates a new situation as compared to 2009 when the previous guideline was adopted (7). The currently available treatment options may have implications for the choice of study population, the goals of treatment, either symptomatic or prevention of disease progression (i.e., bone damage) and for the choice of endpoints, the choice of comparator study duration and time points for evaluation, as well as for the need for adequate discontinuation criteria. To give guidance for the performance of clinical trials and evaluation of drug treatment in axial SpA, a revision of the current guideline taking these new circumstances into account is considered warranted.

3. Discussion (on the problem statement)

The ASAS axial SpA definition will result in the inclusion of patients with earlier/less well defined disease. This will likely result in less external validity of the study results. Misspecification with mechanical non-inflammatory back pain may occur. The validation of imaging scores in nr-axSpA is considered as a challenge. Varying prognosis in the different patient groups may influence study outcome. Treatment in an early phase of the disease may improve prognosis but the risk of overtreatment of patients with a persisting mild disease may alter the ultimate benefit/risk balance.

The GL will discuss how the new ASAS criteria will apply to the inclusion and characterization of patient populations for inclusion in trials for regulatory purposes. It will also discuss the use of newer outcome measures to fulfil regulatory requirements.

The GL will not include aspects of SpA in children since this has been addressed in the Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis.

4. Recommendation

The RIWP recommends that an updated guideline on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis, addressing issues on adequate patient populations and outcome measures for clinical trials.

5. Proposed timetable

The draft guideline may be released for consultation by Q2 2015 and expected to be adopted by 1Q 2016.

6. Resource requirements for preparation

The RIWP will nominate a rapporteur within the group but will relay on the competence of the entire group as well as consulting other WPs or Committees as well as external experts.

7. Impact assessment (anticipated)

An updated guideline taking recent changes in classification and treatment options for patients with axial spondylarthritis into account will facilitate the development of new drugs to meet important medical needs.

8. Interested parties

EULAR, ASAS, national rheumatology associations, patients associations.

9. References to literature, guidelines, etc.

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