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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED FOR A GUIDELINE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INTENDED FOR TREATMENT OF SYSTEMIC AND CUTANEOUS LUPUS ERYTHEMATOSUS

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1. INTRODUCTION

Lupus erythematosus is usually divided into two main types: cutaneous (CLE) and systemic lupus erythematosus (SLE).

The main clinical form of CLE is chronic cutaneous (or “discoid”) lupus erythematosus (DLE). The risk of a patient with DLE to develop SLE is small (1,3% in localised DLE, overall 5-6%, around 20% during the lifetime in disseminated DLE). Despite some haematological and serological abnormalities, patients are in good health. The age and sex distribution of SLE is strikingly different from that of DLE. Therefore, patients with DLE are not a subset of patients with SLE waiting for a disease to develop but can be considered as a separate entity.

There are also patients with other forms of cutaneous LE, such as lupus panniculitis and subacute cutaneous LE; these forms are rare, and more frequently associated with SLE.

DLE is characterised with well-defined erythematous patches with a fairly adherent scale (the forms without scaling are called “lupus tumidus”) which tend to clear with atrophy, scarring and pigmentary changes. The histology is characteristic. Highly potent topical steroids, intralesional steroids, antimalarials (in addition to topical steroids) are given to control the activity of the skin disease and to prevent scarring. Small doses of systemic steroids may be given in some patients.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by production of autoantibodies and involvement of multiple organ systems (SLE 1997 revised American College of Rheumatology classification criteria apply).

SLE appears as a group of related syndromes, with widely varying presentation, body system involvement, and clinical course. The clinical course of SLE is episodic, with activity flares recurring upon increasing disability and organ damage. Corticosteroids (typically prednisone or prednisolone) remain the foundation for long-term control of disease activity, in association with anti-malarials and immunosupressants .Other drugs often used as supportive or adjuvant treatment include analgesics, NSAIDs,, vasodilators (calcium channel blockers, ACE inhibitors) for renal hypertension or Raynaud’s syndrome ischemia, local treatments for rashes or sicca syndromes, transfusions, intravenous globulin for cytopenias, anticonvulsivants, antimigraine medications, anticoagulants for recurrent thromboses, and antidepressants.

High-dose steroids, such as pulse IV methylprednisolone, and immunosuppressants, are standard treatment for management of an acute flare.

2. PROBLEM STATEMENT

Efficacy endpoints for CLE (DLE)

The response to treatment in patients with DLE should assess:

- early signs (erythema, infiltration, hyperkeratosis),
- local spreading of a treated lesion and
- evolution to scarring.

Up to now, there has been no fully validated composite score to assess both disease severity at baseline and response to treatment by taking into account improvement both in early and late signs. Recently proposed CLASI severity index appears to mix early and late signs and therefore does not seem to be very sensitive to therapeutic intervention. Clinically relevant improvement on CLASI score is not well defined and its use in clinical trials requires further discussion.

Efficacy endpoints for SLE

A successful treatment of patients with SLE may:

- improve signs and symptoms of the disease;
- prevent subsequent flares;
- decrease cumulative steroid dose;

- prevent long-term relapse and damage (disease and treatment related).

Possible claims in SLE may therefore be:

1) reduction of signs and symptoms of SLE including SLE flares (reduction in disease activity of SLE);
2) steroid sparing in addition to the reduction of signs and symptoms of the disease;
3) prevention of SLE flares;
4) organ specific claims (such as treatment of lupus nephritis).

Due to the pleomorfic character of the disease and its symptoms, well defined clinical (*e.g.*: organ involvement, immunological, treatments) population criteria should be discussed for each possible claim.

Possible tools:

Measurement of the SLE disease activity -disease activity indices: There are several validated indices in SLE: SLEDAI, SLAM, BILAG, LAI, ECLAM). These indices have been validated in cohort studies as reflecting change in disease activity; no index has been fully validated for the sensitivity for change after therapeutic intervention. In addition there is still disagreement among lupus investigators about the appropriate weights to be accorded to individual components of these scales and how to apply them as responder indices. Moreover, no measure of lupus flare has been fully validated. Therefore, the choice of activity indice(s) in SLE trials requires further discussion.

Measurement of damage: A damage index, such as SLICC/ACR might be of interest.

Measurement of SLE-related quality of life: a choice of disease-specific or general quality of life measures should be discussed.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

It is important to clearly describe acceptable study endpoints to establish efficacy in order to facilitate the development of medicinal products both in SLE and CLE.

In DLE, it is important to assess clinical improvement with adapted tools sensitive to therapeutic intervention; definition of relevant endpoints and clinically relevant response should be elaborated upon.

In SLE, it is uncertain if the SLE activity indices will clearly delineate important clinical responses to therapy in all situations. Some treatments may target single organ system or improve overall disease activity; a targeted claim the choice of primary endpoint should correspond to these expectations. It is also important that a therapy improving one organ system does not worsen a disease elsewhere.

4. RECOMMENDATION

CHMP recommends drafting a guideline on clinical investigation of medicinal products intended for treatment of systemic and cutaneous (discoid) lupus erythematosus. Other forms of CLE (lupus panniculitis, subacute cutaneous LE) are out of score of this guideline.

The recommendation on study designs adapted for different types of claims will be given together with the choice of study population, duration of trials and efficacy endpoints both for DLE and SLE.

5. PROPOSED TIMETABLE

A draft guideline is expected to be released for consultation by 3rd Q/4th Q 2010.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this guideline will involve the EWP. An ad hoc expert meeting may be needed.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is expected that the guideline on clinical investigation of medicinal products intended for the treatment of cutaneous and systemic lupus erythematosus will help to achieve consensus in the evaluation of such products by regulatory agencies. Furthermore, it is expected that the guideline would improve the quality of submitted studies by pharmaceutical industries and facilitate assessment of marketing authorisation applications.

8. INTERESTED PARTIES

- LUPUS Europe
- EULAR (European League Against Rheumatism)