European regulatory aspects on new medicines targeted at treatment of rheumatoid arthritis

Gottfried Kreutz

Within the European Union a remarkable change has been taking place within the past five years that greatly influences the development of new medicines to become marketed products in the whole region or in some of their member states.

It is important for clinicians and basic scientists to realise these changes so that actual requirements be fulfilled by the documents supporting an application for approval in one, several, or all member states.

For this reason the idea of the organisers of this conference was welcomed to provide a forum for discussion between those professionals involved in clinical trials and those who are involved in regulatory decisions by setting up standard requirements or deciding on whether results presented by the applicant are meeting these requirements.

Understanding the organisational structure of the European regulatory house for the evaluation of medicines, the interactions between European institutions involved and to learn about the procedures is the aim of this presentation and all this is referring to rheumatoid arthritis as a major threat to health for many people.

The regulation of Medicines in the European Union is based on the 1957 Treaty of Rome and the Directives 65/ 65/ EEC¹ and 75/318/EEC² as amended by Directive 91/ 507/ EEC with the Commission as the governing institution.

These directives are transformed to national laws and this legal framework forms the regulatory framework of institutions and procedures involved.

Since 1995 the construction of the house is balanced and supported by three major institutional bodies, the Committee for Proprietary Medicinal Products (CPMP), the European Medicines Evaluation Agency (EMA), and the Committee of Heads of Agencies (HoA).

The EMA is providing the organisational, administrative and management facilities for the national agencies and experts to become involved in the European evaluation process and the preparation of decisions.

The HoA group, composed of Directors of national agencies or their directing representatives, are organising and providing regulatory support to make the mutual recognition of a firstly nationally approved medicinal product a reality that is based on critical appraisal of the first approving decision on one hand and comparability of applied criteria on the other.

The CPMP is the group of national representatives (two per member state) to organise and decide on all expertise required to provide scientifically valid answers to all scientific questions of relevance in evaluating medicinal products.

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This is done either within the Committee or by involving working groups of experts permanently assigned as supportive to the CPMP, for example, those for pharmaceutical quality, toxicological safety, clinical efficacy and safety, biotechnological procedures, or pharmacovigilance, or nominated ad hoc as a task force for specific challenges.

Each of these expert groups may involve experts from national agencies or from the scientific community outside of these institutions.

With respect to the field of rheumatology the CPMP has become aware of major efforts in professional groups involved in patient treatment and in pharmaceutical companies to study and develop new medicines providing new approaches with new mechanisms of action and hopes for improved treatment in the future of osteoarthritis and rheumatoid arthritis, two highly disabling diseases with serious health implications to the population.

To make clear on the basis of current knowledge the requirements that have to be fulfilled when a pharmaceutical company applies for approval of a treatment in a specific indication with a pharmaceutical product clinical guidelines on clinical trial methodology have been developed.^{3 4}

The *Points to Consider on Clinical Investigation of Slow-acting Anti-rheumatic Medicinal Products in Rheumatoid Arthritis* is reprinted with permission, as appendix 1. The purpose of a paper like this is threefold:

- to harmonise the view of assessors on the clinical requirements for licensing in this therapeutic area,
- to facilitate transparency of the assessment for products in this therapeutic area,
- to provide useful guidance to the pharmaceutical industry and their experts in planning/ conducting relevant clinical trials in this therapeutic area

The format of a points to consider document that has been chosen here results from the fact that this is a rapidly moving therapeutic area with many still controversial issues. A full guideline would not have been suitable in this situation.

The content will have to be modified according to increases in positive and more widely accepted knowledge. Rheumatologists and scientists contributing to their therapeutic abilities are invited to provide further evidence and sound knowledge.

1 Council Directive 65/65/EEC. OJ No.22, 9.2.1965, P.369/65.

2 Council Directive 75/ 318/EEC. OJ No. L 147, 9.6.1975, page 1.

Bundesinstitut für
Arzneimittel und
Medizinprodukte,
Seestraße 10, 13353
Berlin, Germany

Correspondence to:
Dr Kreutz.

- 3 Points to Consider on Clinical Investigation of Medicinal Products used in The Treatment of Osteoarthritis CPMP/EWP 784/97.
- 4 Points to Consider on Clinical Investigation of Slow-Acting Anti-Rheumatic Medicinal Products in Rheumatoid Arthritis CPMP/EWP 556/95.

Appendix 1

Points to Consider on Clinical Investigation of Slow-acting Anti-rheumatic Medicinal Products in Rheumatoid Arthritis CMCP/EWP/556/95

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Final version

Introduction

Rheumatoid arthritis is thought to be an autoimmune disease, manifested by T-cell activation with release of T-cell derived cytokines and B-cell activation, leading to multiple humoral responses. The main clinical symptoms arise from a chronic fluctuating inflammation of joints. This frequently leads to a progressive, destructive arthropathy resulting in deformities and disability.

The prevalence of rheumatoid arthritis is in the order of 1% of the population. It occurs three times more commonly in women than in men, although this gender difference disappears in later life as the overall prevalence increases. Onset is maximal in the fourth and fifth age decade. Genetic and ethnic influences on prevalence have been identified.

Because of the severity of clinical symptoms and the progressive nature of the disease, the early institution of long-acting medication is now recommended in order to control symptoms and suppress the disease process. Drugs with differing modes of action may be used either alone or in combination.

Features of the disease that are amenable to improvement by existing pharmaceutical means comprise pain, inflammation and loss of mobility. Physical and occupational therapy are applied concomitantly in many patients.

Adverse effects from current anti-rheumatic medication occur frequently, affect various organ systems, and are sometimes serious. Special measures of surveillance and follow-up are required.

It is anticipated that future developments will influence the understanding of underlying pathogenetic mechanisms, the possibilities of inhibiting the natural progression of the disease and thereby significantly improving the outcome.

Also further development of techniques may lead to demonstration of efficacy within a shorter period of time compared to that requested here. Any claim based on these techniques must show convincing evidence, including validation and demonstration of clinical relevance.

Problems requiring attention

1. Scope

This points to consider paper gives guidance on the performance of studies involving the drug treatment of rheumatoid arthritis only. Separate guidance is required for other rheu-

matic diseases such as osteoarthritis, juvenile chronic arthritis, and psoriatic arthritis on account of their differing pathogenesis and natural histories.

Specific aspects of investigation of fast-acting anti-rheumatic medicinal products are not covered in this points to consider paper.

2. Treatment of R.A. and potential claims

The aims of treatment of R.A. are:

- to relieve pain
- to improve or sustain function
- to decrease inflammatory synovitis
- to prevent structural damage

The four goals should be assessed by objective measures or scales/scores all of which have to be validated. Which of these goals are incorporated into study protocols depends on the nature of the agent being studied. For example, for a structure modifying agent aimed at preventing structural joint damage it would be expected that all four goals be studied. However, for an anti-inflammatory agent or a pain relieving agent not expected to demonstrate structure modifying effects inclusion of measures to monitor structural joint damage is valuable only when clinical safety is a concern in that respect. To prevent secondary complications (unavoidable side effects of effective treatment such as adverse glucocorticosteroid effects) can be an additional aim provided this has been established as an additional aim before commencing study by application of appropriate methods.

Regulatory approval of any claims made by the applicant will be determined after assessment of the efficacy measures documented in an appropriate manner.

3. Classification of anti-rheumatic therapies

The concept proposed by the 5th ILAR/WHO task force in 1993 although not universally accepted or entirely free of problems of definition or delineation is slightly changed and provides a working approach to the development of drugs capable, not only of influencing symptoms and signs of the disease but also of modifying the disease process either directly or indirectly.

ANTI-RHEUMATIC THERAPIES

- Symptom-Modifying Anti-Rheumatic Drugs (SMARD)
  - Nonsteroidal Antiinflammatory Drugs (NSAID)
  - Corticosteroids
- Disease-Modifying Anti-Rheumatic Drugs (DMARD)
  - non-cytotoxic (antimalarials, gold, sulphasalazine, D-penicillamine etc.)
  - cytotoxic (MTX, cyclophosphamide, chlorambucil etc.)
- Disease-Controlling Anti-Rheumatic Therapy (DCART)

This classification is consistent with a classification given by a group of European experts, describing categories Type A (symptom modifying), B (inflammation modifying), and C (structure modifying).

According to this classification a Disease-Controlling Anti-Rheumatic Therapy (DCART) must demonstrate convincingly the arrest of existing structural erosions or the prevention of new ones, together with other evidence of delayed disease progression or improvement of outcome measures. At present this has not been adequately demonstrated with any of the currently available treatments.

4. Tools to measure efficacy (primary or secondary endpoints)

- a. swollen joint count (28 joints or more)
- b. tender joint count (28 joints or more)
- c. physician's global assessment of disease activity
- d. patient's global assessment of disease activity
- e. pain score (patient's assessment of pain, VAS)
- f. acute phase reactants (erythrocyte sedimentation rate, C-reactive protein)
- g. physical function including morning stiffness (assessed by patient, e.g. HAQ, AIMS)
- h. x-ray (joint space, erosions, e.g. Larsen, modified Sharp)

These efficacy measures a to h refer to the following classification categories (see 3.) and should be studied accordingly:

classification category	primary endpoints	secondary endpoints
SMARD (A)	e, g	a, b, c, d, f
DMARD (B)	a, b, g	c, d, e, f
DCART (C)	g, h	a, b, c, d, e, f

It is very important that response criteria are adequately justified, chosen before the study is started, and thresholds are predefined.

Where combined measures are used to document efficacy only validated composite endpoints (e.g. DAS, Paulus, ACR 20) are acceptable as additional endpoints and results need to be consistent with the single efficacy endpoints described.

Agents which are claimed to prevent structural joint damage (the hallmark of the DCART), need to demonstrate radiological differences on the basis of before/after comparisons taken not less than one year apart using full randomisation and pre-agreed criteria.

Slowing of radiographic progression does not in itself define a patient benefit, demonstration of such an effect is considered to be a surrogate for long-term clinical benefit. However, there is good indirect evidence that, by favourably modifying the natural history of rheumatoid arthritis in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients. It would be expected that an applicant will provide additional evidence to support this surrogacy.

For clinical safety reasons (e.g. anticipation of deleterious effect on joint cartilage) it may be advisable to perform x-ray examinations in studies involving other than DCART.

Future development of radiological techniques, x-ray or MRI, may lead to increased sensitivity of methods.

Where the MRI is used to document efficacy clinically relevant changes should be defined in advance, as this technique is not established as a validated measure of anti-rheumatic drug efficacy.

5. Supportive evidence for efficacy

- a. synovial biopsy and histology
- b. cell markers (lymphocytes, chondrocytes)
- c. intraarticular cytokine concentrations
- d. emotional and social function (e.g. IRGL)
- e. quality of life
- f. extra-articular complications/symptoms

Of the above list only d) and e) are established as useful additional secondary endpoints. Where any of a) to c) or f) are used, their use must be justified.

Other features such as chondroscopy, scintigraphy, ultrasonography, other biochemical measurements (serum, urine, joint fluid), extra-articular manifestations of R.A. (e.g. nodules, vasculitis) or concomitant disease (e.g. cardiovascular disease, lymphoma) may also be used as supportive evidence for efficacy but only when the methods have been subjected to prior validation and their clinical relevance predefined.

6. Comparator

6.1 PLACEBO

The absolute efficacy of DMARD products should be established by means of placebo controlled trials. Since it would be unethical to retain a patient with rheumatoid arthritis on placebo treatment indefinitely, the duration of placebo control must necessarily be limited. Six months is acceptable.

In the case of a potential DCART, using existing validated technique, i.e. x-rays,

6 months would be insufficient time to demonstrate efficacy in terms of endpoints relevant to the DCART claim. Because of the difficulties associated with the use of placebo control for these longer periods of time, alternative design strategies must be pursued (see 9.).

6.2 ESTABLISHED COMPARATOR

Comparative studies against established comparator for DMARD (e.g. Methotrexate, Sulfasalazine) should also be undertaken. A demonstration of the superiority of the test drug to an appropriate comparator in at least one study is more persuasive of its efficacy than a demonstration of equivalence.

6.3 COMBINATION THERAPY

Treatment with combination of different medicines is gaining popularity in patients in whom monotherapy has failed. Add-on placebo therapy may also be used when study design requires placebo and allows for combination with other effective treatment. Rescue medication, if allowed for as a combination therapy should be predefined in the study plan.

7. Duration of exposure

The required duration of exposure depends largely on the chosen endpoint, the sensitivity of applied and accepted assessment methods,

and the nature and the magnitude of the effects of the agent studied.

In order to demonstrate efficacy in radiological terms using technology currently generally available, an observation period of not less than 1 year is required. This duration must be previously defined and related to the clinical relevance.

Anti-inflammatory effects on the other hand may for example be evaluated within several months.

8. Numbers of patients requiring long-term exposure

To assess clinical safety and identify relevant adverse reactions an observation period of not less than twelve months is required. Taking into consideration the chronicity of the disease and the need for long-term treatment longer periods may be more appropriate.

A minimum of 300 to 600 patients should be exposed to the proposed marketing dose for 6 months and at least 100 patients exposed at this dose or above for a minimum of 12 months. Appropriate efficacy and clinical safety measures should be adequately monitored for this period.

9. Study design

In this disease only the parallel group design is acceptable as a means of assessing efficacy and safety. Crossover trials are not acceptable because the progressive nature of the disease makes it impossible for the patients to be in an equivalent state at the start of each treatment period. In addition carry-over effects of treatment from one period to the next are difficult to avoid. Furthermore, in treatment periods after the first, delayed adverse effects from the previous period may be confused with any lack of efficacy of the treatment in the current period because disease symptoms and adverse effects may coincide.

When designing a parallel group trial for a potential DMARD claim, careful consideration should be given to the choice between a two arm study design (verum, placebo) and a three arm study design (verum, active DMARD comparator, placebo) the appropriate duration of treatment being 6 months. There are two recognised alternatives for the design of a parallel group trial for a DCART. One is a two-arm study comparing the new agent with an established DMARD, seeking to show that the DCART is superior to the DMARD in terms of relevant endpoints. The other is a two-arm study in which patients in both arms receive an established DMARD but are

randomised to receive in addition either the new agent or placebo. Both of these designs allow the continuation of randomised therapy for sufficient time to establish effects on endpoints recognised as specific for DCART activity. In all of these designs current ideas favouring early treatment should also be taken into account.

In order to explore the degree to which treatment effects are sustained in the long-term, a study design may be employed in which efficacy measures are observed after randomised and blinded withdrawal from a long period of treatment.

10. Target population

Observable effects of treatment are dependent on diagnostic criteria applied to patients when entering a study and disease related factors such as stage of disease, duration of disease, or disease activity have to be documented appropriately, using predefined criteria. Because there are no generally accepted predictors for progression of the disease and responsiveness to treatment patients have to be fully and carefully documented in all respects. Thus initial symptoms of active disease (joint pain, morning stiffness), functional status and limits of joint movement, disease activity (ESR, Synovitis, CRP), radiographs, non-articular symptoms, and concomitant diseases all have to be recorded.

Other treatment modalities interfering with study treatment are of particular importance. Careful registration for example of concomitant non-pharmacological treatment (physical therapy of various types etc.) has to be performed and medication for diseases other than rheumatic must be completely documented.

Whenever possible it is recommended that these treatments be standardized and previously defined.

11. Interactions

Due to the high proportion of patients using anti-rheumatic therapy other than the one studied or pharmaceutical treatment other than anti-rheumatic because of comorbidity, interaction studies regularly have to be performed. Selection of substances for conducting interaction studies should be based on the known pharmacokinetic and pharmacodynamic properties of the agent studied, the existing anti-rheumatic agents, and other possibly interacting medications. Recommendations from the guideline on interactions have to be taken into account.