Proposal for a European multicenter study -
scientific, logistic and financial aspects

We propose to conduct a multicenter therapeutical trial in patients with idiopathic polymyositis and dermatomyositis. This study will investigate the value of methotrexate added to treatment with glucocorticoids. The clinical, laboratory and biopsy materials obtained during the trial will serve as a basis for future research studies and will enable to European investigators to form a network with well-defined patient’s data. This should establish strong possibilities for collaborative research in this field in the future and enhance the potentiality to support such collaboration within the framework of European Union research programmes. The trial will require interactions and meetings between investigators to standardise the outcome procedures and these interactions will further promote collaboration between EULAR members.

The original protocol submitted to EULAR previously has been re-written into assessor–blind version, which would eliminate the need for blinded packaging of methotrexate and placebo.

We propose to organize the trial in the following format:

**The title of the study:** “A prospective, randomised, assessor-blind, multicenter study of efficacy and safety of combined treatment of methotrexate + glucocorticoids versus glucocorticoids alone in patients with polymyositis and dermatomyositis.”

**Acronym:** PROMETHEUS (Polymyositis and Dermatomyositis Research on Methotrexate in European Study).

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Therapeutic trial in patients with idiopathic polymyositis and dermatomyositis is proposed. The study will investigate safety and efficacy of combined methotrexate + glucocorticoids treatment compared with glucocorticoids alone.

A total number of 50 patients with polymyositis/dermatomyositis will be randomised into two groups (1: Methotrexate + glucocorticoids and 2: glucocorticoids only). Patients will be equally distributed between the two groups providing 25 patients per treatment arm. The randomisation will be based on random numbers generated by a computer program. After being enrolled in the study, the patients will receive 12 months of therapy followed by a 12-month follow-up period.

The primary endpoint is the total dose of glucocorticoids (calculated in mg/kg weight), which will be administered for 12 months between baseline and the end of treatment.

There are several secondary objectives, which will be pursued during and after the trial. Disease activity and damage will be prospectively assessed by the newly proposed tools by IMACS (International Myositis Assessment and Clinical Studies Group) (1, 2). Other secondary objectives comprise: muscle endurance (3), glucocorticoid related side effects. functional ability measured by HAQ, quality of life by SF-36, and number of patients with treatment failures. The other aims will also include (i) search for reliable prognostic parameters in the further prognosis of patients with inflammatory myopathies and (ii) studies on the pathogenic aspects of inflammatory myopathies. The investigations of serum, lymphocytes, muscle tissue and MRI will be organized. DNA and RNA will be stored for future genetic studies.

Patients with definite or probable polymyositis or dermatomyositis diagnosed according to diagnostic criteria will be enrolled (4, 5). They will have disease activity that according to physician’s own judgement requires high dose immnosuppressive treatment (based on clinical assessment of weakness, elevation of muscle enzymes and, if available, on magnetic resonance imaging findings). Patients should be previously untreated with the exception of significant (> 20 mg Prednisone daily) glucocorticoid treatment up to 8 weeks. Patients with other than primary idiopathic polymyositis or dermatomyositis, such as drug-induced myositis, myositis clearly in association with other connective tissue disease, inclusion body myositis, malignancy related myositis, and juvenile dermatomyositis will be excluded.

All patients will start with prednisone 1 mg/kg/day and the dose will be tapered if patients meet definition of improvement, which has been proposed by IMACS group and also if the treating physician considers appropriate to decrease steroids. Methotrexate will be administered orally, once weekly, with a starting dose 10 mg. This will be increased gradually to 20 mg/week if tolerated by week 5 with a potential to further increase to 25 mg/week in 12 weeks visit. Patients will be first assessed after 2 weeks and then monthly for a period of 48 weeks. There will be a follow-up after a further 1 year in order to find out the impact of the early treatment on the long-term disease outcome.

All efficacy analyses will be performed using intention-to-treat population (ITT). In addition, the primary and secondary variables will be analysed using the per-protocol population, which will contain all patients in the ITT population, who also reached Week 48 of treatment without any major protocol violations. The safety population, which will contain any patient who received at least one dose of study drug, will be used for all safety analyses.
Polymyositis and dermatomyositis (PM/DM) are rare, chronic disorders that may lead to substantial long-term morbidity, reduced quality of life, work disability and mortality. The prevalence of the disease is reported between 2-10/100 000 and average annual incidence rate is about 7-8/100000 (6), although it seems that the frequency of cases is increasing, either due to real higher incidence or due to greater awareness of the disease. The cause of the disease is not known. PM/DM are allocated to a group of connective tissue diseases from several reasons: (i) they may associate with other disease entities from this group, (ii) they are accompanied with a number of immune system disturbances, including autoantibodies, and (iii) they react, to a certain extent, to glucocorticoid and immunosuppressive treatment.

The development of effective and safe treatment protocols for PM/DM has been hampered by its relative rarity; the absence of standardized assessment methods and limited previous collaboration between European centers in clinical trials. Current treatment of PM/DM is centered on using high dose systemic glucocorticoids. However, no controlled study was performed to show usefulness of this treatment and, from ethical reasons, it is unlikely that such study will ever be performed. Even the dose of glucocorticoids is debated, as some retrospective studies show equivalence of medium doses to high doses with respect to survival (7) or functional outcome (8). Unfortunately, with this glucocorticoid therapy very few adult patients with PM/DM recover muscle function. Approximately one third of cases do not respond at all to glucocorticoid treatment. In addition side effects from glucocorticoids such as osteoporosis and fractures are major problems, which contribute to long-term disability (9, 10).

There have been only few randomized controlled trials of drug therapies in PM/DM. It is necessary to realize that due to the rarity of the disease these trials included only low numbers of patients:
- 16 patients in a double blind trial with azathioprine + prednisone as initial treatment of PM patients (comparison between two groups, each consisting of 8 patients), which showed improvement in functional ability at 1 and 3 years after initiating treatment (11, 12)
- 39 patients in a trial with plasmapheresis and leukapheresis (each group consisted of 13 patients), which failed to show efficacy (13)
- 15 patients in the administration of high i.v. immunoglobulin doses (two groups, 8 and 7 patients), which demonstrated beneficial effect in DM (14).
- 30 patients (each group had 15 patients) in the cross-over study which showed superiority of a combination therapy with azathioprine and methotrexate to high dose of intravenous methotrexate with leucovorine rescue (15).

These clinical trials have failed to provide conclusive results because they have been underpowered and involved too few patients. Furthermore, no standard evaluation has been used in efficacy assessments and therefore it is impossible to compare the relative benefit of the various treatment modalities.

As a consequence current treatment recommendations are mainly based upon case reports, open studies, retrospective evaluations and empirical evidence. These suggest treatment efficacy and steroid sparing effect of methotrexate (9, 16). Equally little, or even less is known about cyclosporine A, cyclophosphamide, chlorambucil, tacrolimus, or fludarabine. A recent open study showed improvement in 70% of patients treated with intravenous immunoglobulins (17). We have performed an open randomized trial in which we compared methotrexate with cyclosporine A in addition to glucocorticoids in 36 patients with PM/DM (18). Our results showed a tendency to a better effect of methotrexate in some parameters.

Despite that methotrexate is now probably the most frequently used immunosuppressive drug in PM/DM, such therapy has not yet been studied thoroughly and properly evaluated in a randomised controlled trial. Furthermore, data is lacking on the time point of methotrexate addition, with frequent suggestion to start such treatment only when glucocorticoids fail. In analogy with the better effect of early aggressive treatment in rheumatoid arthritis, such treatment should be rather considered in the early phases of the disease. Actually there is some data showing that the prognosis of the patient is worse if the treatment is delayed (9), and a recent small open study showed better outcome for patients with juvenile dermatomyositis treated early with combination of low dose methotrexate and intravenous methylprednisolone (19).

Therefore, the information on the relative efficacy and benefit of methotrexate administered from the early stages of the disease is important. This importance is supported also from the perspective of imminent future studies that are likely to be conducted in these patients with various biological agents, so far mostly given together with methotrexate in studies in RA. The proper evaluation of methotrexate treatment and its risks during a long-term administration should be known before commencing larger trials with such a therapy in myositis.

Another problem in myositis is the lack of reliable prognostic parameters. The worse disease duration and outcome is usually anticipated in patients with dysphagia, pulmonary involvement, high initial disease activity, delay in treatment, and in those with certain autoantibodies. However, the question is how applicable are some of these parameters to general population of patients within Europe, as e.g. we and others see very mild disease with excellent outcome in some patients with the unequivocal presence of anti-SRP antibodies,
whose prognosis is normally considered to be very poor. This applies to a similar extent to patients with anti-Pm-Scl and to some patients with anti-Jo-1 antibodies.

**Summary of main research objectives:**

1) Because no controlled study with methotrexate has been performed in PM/DM, this will be the first controlled, randomized study with MTX in myositis.
2) Because no data is available on the time point of methotrexate addition, this study will evaluate methotrexate given to patients at the early stages of disease.
3) The effect of the two treatment approaches will be evaluated on the long-term disease outcome.
4) Entry criteria should ascertain that consistent groups of patients will be evaluated.
5) Newly proposed clinical assessment tools will be evaluated in the framework of the clinical study.
6) Sub-study assessing the effect of treatment on muscle pathology changes will be organized.
7) Prognostic parameters based on the presence of autoantibodies and genetic markers will be evaluated.

**Justification for pan-European collaboration**

Myositis is a rare disease and in no single country a clinical therapeutic study on the sufficient number of patients can be performed. These patients need to be well defined to assure homogeneity, which is necessary for reliable assessments. A therapeutic study will enhance the collaboration of European centres interested in myositis research. It is anticipated that this new established network will be used for future scientific projects in myositis.

**Relevance of the project, strategic objectives and milestones, resources:**

Project is proposed to assess the contribution of addition of methotrexate to glucocorticoid standard treatment in myositis.

The strategic objectives include methotrexate efficacy, early treatment, long-term outcome, improvement in contacts of European researchers and clinical units dealing with myositis patients, assessment of the newly proposed clinical tools and initiation of a number of side studies, such as autoantibody investigation, muscle biopsy evaluation before and after the treatment, MRI studies, DNA and RNA analyses.

Milestones include development of the study protocol, information for subjects and informed consents, case report forms; identification of sponsor and study centers; preparation of study drug material and labelling; organization of monitoring and pharmacovigilance; insurance; application for approvals from competent authorities and ethics committees.

Further milestones include initiation of the study, enrollment of the first patient, enrollment of all patients, data entry and processing, statistics, study closure, publication.
Sub-studies on pathogenetic aspects, autoantibodies and prognostic markers.

Resources. Investigators have initiated the study and prepared protocol, case report forms, informed consents and other administrative requirements for the study. Research grant from EULAR is sought for the study conduct. This will be complemented by resources derived from EU supported Autocure project and by local support from individual investigators.

**Organisation**

The study has been prepared in collaboration between Institute of Rheumatology, Prague and Rheumatology Unit, Karolinska Institutet, Stockholm. The data for randomization will be sent from the participating center to the Institute of Rheumatology where the randomization number will be assigned and faxed back. Copies of case report files will be mailed or filled online regularly into the Institute of Rheumatology, where the completeness will be checked. Data will be monitored.

Statistical evaluation and supervision will be performed by medical statistician in the Institute of Biostatistics and Analyses, Masaryk University, Division of Clinical Studies, Jana Uhra 10, 602 00 Brno, Czech Republic.

Both coordinating centres in collaboration with all participants will organize the research parts, evaluation of the results and publications.
Logistic aspects and timeframe for the study:

1) Final protocol, informed consent in English, paper CRFs already prepared. The possibility of electronic CRF will be explored by the end of September 2007.

2) Insurance: it will have to be closed in centres individually. We have a proposal in the Czech Republic from the Insurance Company for 900 Euro/year, which can be finalized in days.

3) Application to competent authorities. First, sponsor’s application has to be submitted. This means that application to CA will be sent in the Czech Republic by the end of July 2007. Applications for the centres will be prepared by the coordinator in Prague using the standard forms required by EMEA and sent to centres.

4) Ethics committees. Application in the Institute of Rheumatology will be submitted by the end of July 2007. Applications for the centres will be prepared by the coordinator in Prague using the standard forms required by EMEA and sent to centres.

5) List of participating centres - end of October 2007. All necessary materials for CA and EC submissions will be delivered to the centres by the end of November.

6) Agreements with participating centres – by the end of February 2008.

7) Agreement with Institute of Biostatistics and Analyses for data entry and data processing – by the end of October 2007.


9) Enrolment period 2 years

10) Last patient/last visit January 2011.
**Budget**

A sum of 190 000 Euro for the 3 years is requested for study support. Altogether 10 or more centers will participate in the study. The support is sought primarily for conduct of the study itself and expenses that will be incurred in organization and running of the study as well as in assessment of the results. The interactions between investigators are planned, however, these will mainly occur at the EULAR congress or other scientific meetings attended by a majority of the investigators. Some support, however, need to be planned for sites not attending this type of meetings. There is some support for individual sites per patient basis, which is mainly meant for support of study nurse and basic laboratory tests in centres, where this cannot be done as a part of routine testing. Additional support for studies on autoantibodies, pathology and genetics will be sought from different sources.

The following main items are calculated for the budget:

1. Payment for the state authorities (regulatory competent authority, health agency) and ethics committees (multicenter, local) for the study approval. The requirements (with respect to costs and also with respect to authorities to be applied for approvals) differ substantially between different European countries. As a mean for each centre (country) the following approximate costs are calculated: competent authority (1000 EUR), ethics committee - multicenter (1500 EUR), local EC (550EUR); x10 centre = 30 000EUR
2. Insurance for the trial
   - for each centre approximately/1 year 1500 EUR x 2years x10 centre = 28 000EUR
3. Study personnel to organize the trial and interaction between centers, pharmacovigilance – approx. 22 000EUR
4. Support of study conduct in individual centers 500 Euro/patient (study nurse, pharmacy, lab tests) = 50000 Euro.
5. Monitoring (salary 12 500EUR/year x 2year = 25 000EUR, traveling expenses (airplane tickets, hotels etc.) 15 000EUR = 40 000EUR
6. Support for the necessary administrative management - approx. 2500EUR
7. Transport of various laboratory materials (serum, DNA, biopsy material) into core laboratories 3000 EUR
8. Postage, telephone, fax and stationary, electronic CRFs - 2 500 EUR
9. Investigator’s meetings + Travel expenses to meet approx. 10 000EUR
10. Data entry, data processing, support for the statistical evaluation of the results - 4000 EUR

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Total 1st year: 86 000 EUR

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Total 2nd year: 63 000 EUR

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Total 3rd year: 41 000 EUR

Total per project: 190000 EUR.
IMPLEMENTATION AND RELEVANCE OF THE PROJECT FOR EULAR

Polymyositis and dermatomyositis are rare diseases and it is notoriously difficult to perform clinical studies in these patients. The primary goal of the trial is to improve the approach to patients with polymyositis and dermatomyositis with testified knowledge that our frequently used combined immunosuppressive treatment really is more beneficial to patients with a reasonable benefit/risk ratio. As the disease is usually long-term and the consequences of the treatment might appear late in the course of the disease, the study is sufficiently long to appreciate such effects. In the end we should be able to give evidenced information to our patients with respect to efficacy and long-term side effects of the two treatment options.

The important aspect in implementing the trial is that it will require intensive collaboration and frequent interactions between several European investigators and centres working with myositis patients. The clinical, laboratory, biopsy and other materials obtained during the trial will serve as a basis for a number of future research studies and will enable to European investigators to form a network, which will be using the accumulated well-defined patient’s data. This should establish strong possibilities for collaborative research in this field in the future and enhance the potentiality for applications to support such collaboration within the framework of European Union research programmes.

Important developments have been recently achieved in the area of the activity and damage assessment in polymyositis and dermatomyositis. These endeavours have been driven mainly by investigators from the USA and London, with active participation of representatives from the coordinating centres of the proposed trial. The assessment of the tools in a prospective trial is now necessary. Their obligatory use in our trial should also stimulate the spread of these newly proposed tools for disease assessment to the more fast adoption between EULAR members. This is the first and necessary step to obtain comparable data in the future. Also the criteria for improvement and for worsening have been proposed and our trial will be helpful in their evaluation. It will also provide strong basis and arguments for EULAR members to actively participate in the discussions and future developments in the area of polymyositis and dermatomyositis.
REFERENCES


