EULAR GRANT PROPOSAL: ASTIS-TRIAL (extension)

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Applicant: Scleroderma Study Group of the Working Party Autoimmune Diseases.

Chairpersons: JM van Laar, D Farge, A Tyndall

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The ASTIS Trial is a multicenter randomized controlled phase II/III study conducted under the auspices of EULAR/EBMT. The aim of the trial is to compare safety and efficacy of high dose immunoablation and autologous hematopoietic stem cell transplantation (HSCT; considered the investigational treatment) versus monthly intravenous pulse-therapy cyclophosphamide (considered the control treatment) in patients with diffuse systemic sclerosis at risk of premature mortality. The primary end point is event-free survival defined as the time from randomization until the occurrence of death or the development of persistent major organ failure (1).

The trial was launched in 2001, the 1st interim analysis on 20 patients enrolled was completed in 2004, and the 2nd interim analysis on 66 patients enrolled was completed in June 2006, confirming the feasibility of the treatment regimens and demonstrating absence of unexpected toxicities (2).

At the time of this writing 84 patients have been enrolled in 20 European centers. The total number of patients needed to detect a statistical difference between the 2 study arms has been recalculated to be 120 with a minimum study duration of 3 years per patient.

The trial will yield valuable information on the outcome of patients with severe systemic sclerosis after stem cell transplantation versus conventional chemotherapy, and on pathogenetic aspects of the disease.
NEED AND RELEVANCE OF THE PROJECT

Need
Patients with severe diffuse systemic sclerosis are at risk of premature morbidity and mortality, especially when cardiac, pulmonary, renal or intestinal involvement is present. No treatment has been proven to be effective in preventing major organ failure or death (3). Recently published placebo-controlled prospective trials have shown modest efficacy of cyclophosphamide-based regimens on lung function and skin thickening, confirming data from earlier retrospective analyses and small open studies (4-10). The paucity of sufficiently powered clinical trials in systemic sclerosis can partially be explained by the low incidence of severe systemic sclerosis, which translates in low median number of subjects enrolled in non-industry sponsored studies. These notions underscore the importance of sufficient funding and of international, multicenter collaboration in non-industry sponsored clinical trials in an orphan disease like systemic sclerosis. Previous EBMT/EULAR registry analyses of transplants in patients with systemic sclerosis have demonstrated the feasibility and potential efficacy of high dose immunosuppressive therapy and autologous stem cell transplantation and illustrated the importance of standardized assessment, uniform entry criteria and treatment regimens (11-13).

Relevance
The relevance of the present project is underscored by the need to develop disease modifying therapies for patients with severe systemic sclerosis through multicenter collaborative efforts.
At the recent 2006 ACR meeting in Washington DC, the concept of HSCT in SSc was supported in several state-of-the-art lectures from independent experts.
A similar study has been launched, sponsored by the NIH (A Tyndall is on the DSMB) with major financial support, exploiting much of the experience gained in Europe and sofar in the ASTIS trial. EULAR has at the moment a distinct leading role in this field.

STRATEGIC OBJECTIVES AND MILESTONES

Strategic objectives
The strategic objective of the ASTIS trial investigators group is to foster collaboration of European centers with expertise and interest in the management of patients with systemic sclerosis, in particular the exploration of high dose immunosuppressive therapy and autologous stem cell transplantation as a potential therapy for patients with severe systemic sclerosis. A successful outcome of the trial may lay the groundwork for future non-industry driven multicenter trials to optimize disease modifying therapies of patients with systemic sclerosis.
A positive decision to fund ASTIS by EULAR may increase chances to obtain future funding through NIH or EU, e.g. to conduct side studies.
**Milestones**
Past, present and future milestones are defined as follows:

- **2001**: formation of a core study group to design the protocol, case record forms, and website.
- **2001-2002**: enrollment of the first cohort of 20 patients.
- **2003**: completion and approval of the 1st interim-safety analysis marked successful completion of the pilot phase.
- **2002-2005**: enrollment of the second and third cohort of 20 patients each.
- **2006**: completion of the 2nd interim-analysis on 66 patients, approved by the Independent Data Monitoring Committee.
- **2007**: planned 3rd interim-analysis on 85 patients.
- **2008**: expected completion of accrual of target number of 120 patients.
- **2010**: presentation and publication of early results.

Investigators’ meetings were held in Paris in 2005 and in Leiden in 2006 to discuss enrollment, clinical issues, and funding opportunities.

Updates of the trial were presented at the EULAR-meetings in Berlin (2004) and Amsterdam (2006).

**RESOURCES, BUDGET AND ORGANISATION**

**Resources**
The pilot phase of the trial was sponsored by an unrestricted grant from AMGEN Europe, Sangstat, and the Horton Foundation (Switzerland), which was spent on the production of case record forms, development of a database, and collection and entry of data in a central database (Hesperion, Basel, Switzerland).

A EULAR-grant of 50k EURO was awarded in 2005 to compensate for trial administrative costs of the 3rd cohort of 20 patients (patients 61-80).

Treatment with pulse therapy cyclophosphamide is reimbursed by health insurance companies in most participating centers. In 2006 a deal was made with Miltenyi Biotec to provide CliniMACS (CD34-selection) columns at a 50% discounted price. Reimbursement of extra costs related to the transplantation procedure (e.g. CD34-selection columns, ATG), currently amounting to EURO 7,500 per patient, is presently arranged on a local level.

**Budget**
To ensure successful completion of the trial a final financial injection of 50k EURO is deemed necessary based on the following estimates:

- **Study Administration Office**: 5k
- **Compensation for local trial administration (1k/pt)**: 40k
- **Site visits to ensure data quality**: 5k
Organisation
The trial is conducted under the auspices of the EBMT Working Party Autoimmune Diseases (currently chaired by R. Saccardi) and the EULAR Standing Committee for International Studies Including Therapeutic Trials (ESCISIT, chaired by M Dougados. The trial is chaired by JM van Laar (Leiden, The Netherlands), D. Farge (Paris, France) and A. Tyndall (Basel, Switzerland).
Trial management is carried out by the Study Administration Office (SAO) currently located in Leiden. Data from participating centers are submitted to the SAO, run by a trial manager under supervision of the Study Chairpersons. The Study Chairpersons advise on eligibility of patients and on medical issues and supervise conduct of the trial.
The study statistician (J. Sont) has conducted the interim analyses, and is responsible for the final statistical analyses of the trial. The reports arising from the interim analyses were reviewed by three independent experts (D Furst, USA, F Wollheim, Sweden, J Apperley, UK), who advised the Study Chairpersons on the conduct of the study. Concise versions of the reports are then provided to participating centers (see attachment).

The following centers (+ local study investigator) have contributed so far by enrolling patients:

**Austria:**
Allgemeines Krankenhaus Wien, Vienna (Dr. Machold),

**France:**
Groupe Hospitalier St. André, Bordeaux (Prof. Constans), Centre Hospitalier Universitaire de Clermont Ferrand (Prof. Philippe), Unité A, CHU de Grenoble (Dr. Sarrot-Reynaudl), Hopital Claude Huriez, Lille (Prof. Hatron), Hôpital St. Marguerite, Marseille (Prof. Durand), Hôpital Saint-Louis, Paris (Prof. Farge), Hôpital de Hautepierre, Strasbourg (Prof. Sibilia), Hôpital Purpan, Toulouse (Prof. Adoue), CHU Pierre Zodba, Fort de France (Prof. Arfi), CHU la Milétrie, Poitiers (Prof. Roblot), CHU de Montpellier, Montpellier (Prof. Quéré),

**Germany:**
Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt (Prof. Kaltwasser), Albert-Ludwigs-Universität, Freiburg (Prof. Peter), Medizinische Universitätsklinik und Poliklinik Tübingen (Prof. Kötter), Medizinische Universitätsklinik und Poliklinik Würzburg (Prof. Tony), Universitätsklinik der Rhur-Universität Bochum/Herne (Prof. Rump, dr. Weiner),

**Greece:**
G Papanikolaou Hospital, Thessaloniki (Dr. Fassas),

**Italy:**
University of Florence (Dr. Saccardi, Prof. Matucci)

**Switzerland:**
Felix Platter-Spital Basel (Prof. Tyndall, Prof. Gratwohl), Insel Spital Bern (Prof. Villiger),

**The Netherlands:**
Leiden University Medical Center, Leiden (Dr. van Laar), Universitair Medisch Centrum St. Radboud, Nijmegen (Dr. van den Hoogen), VU Medical Center, Amsterdam (Dr. Voskuyl),

**United Kingdom:**
Leeds General Infirmary, Leeds (Prof. Emery)
Scientific side studies linked to the ASTIS trial will be done by groups in France, Italy, The Netherlands, Switzerland, and the UK. Topics include: immune reconstitution, CT-measurement of lung fibrosis, myocardial scintigraphy, biomarkers of fibrosis and endothelial activation and analysis of skin biopsies. Funding for side studies is arranged by the responsible investigators.

IMPLEMENTATION AND RELEVANCE FOR EULAR

**Implementation**
The ASTIS trial may provide conclusive information on the best of two treatment strategies for patients with severe systemic sclerosis: repeated moderate dose immunosuppression versus intensive immunosuppression and autologous stem cell transplantation. It will also provide valuable information for further studies: selection of primary and secondary study parameters, clinical relevance of biomarkers and immunomonitoring.

In case the transplant arm proves superior in terms of safety and efficacy, a network of EULAR/EBMT-transplant centers may be accredited as centers of expertise in the treatment of severe systemic sclerosis. If the control arm proves superior a network of scleroderma treatment centers can also be envisioned coordinated under the auspices of EULAR and embedded in EUSTAR.

**Relevance**
A successful outcome of the ASTIS trial may provide an impetus for further collaborative clinical trials in Europe, contributing valuable expertise and experience in trial organisation, protocol development and trial administration.

It is expected that EULAR will benefit from positive publicity that will arise from its association with ASTIS, being the first investigator-driven European randomized clinical trial in scleroderma.
REFERENCES (those related to the EBMT/EULAR Scleroderma Transplant activities are marked with *):