EULAR GRANT PROPOSAL: ASTIS-TRIAL

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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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ABSTRACT

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 during the study period of 2 years. The trial was launched in 2001, and an interim analysis on the first 20 patients enrolled was completed in 2003 demonstrating the feasibility of the treatment regimens selected as illustrated by the absence of unexpected toxicities or treatment related mortality in either arm. At the time of this writing 42 patients have been enrolled in 16 European centers. The total number of patients needed to detect a statistical difference between the 2 study arms was 160 based on the original power calculations, but will be adjusted based on the upcoming interim analysis. The trial may yield valuable information not only on the outcome of patients with severe systemic sclerosis after stem cell transplantation versus conventional chemotherapy, but also 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. Retrospective analyses and small open studies have suggested cyclophosphamide-based treatments may be effective in this respect, but data from controlled trials are lacking. 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. A recent EBMT/EULAR registry analysis of transplants in patients with systemic sclerosis has 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.

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 2004 ACR meeting in San Antonio and ASH meeting in San Diego, the concept of HSCT in SSc was supported in several state-of-the-art lectures from independent experts.
A similar study is being planned by the NIH (A Tyndall is on the DSMB) with major financial support and exploits 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 succesful 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 funding through NIH or EU, e.g. to facilitate 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.
2003: an interim-safety analysis marked succesfull completion of the pilot phase.
2002-2004: enrollment of the second cohort of 20 patients. An update of the trial was presented at the recent EULAR-meeting in Berlin in the session of ‘Cutting edge in Rheumatology’ and collaboration with the EUSTAR-group initiated. 2005: The second interim-analysis on 40 patients will herald the launch of promotional activities to expand the number of centers involved and enhance awareness about the trial among patients and specialists by sending out letters to rheumatologists, internists and dermatologists in countries with participating centers. An investigators meeting will be scheduled to discuss enrollment, clinical issues, and funding opportunities. 2005-2007: continued enrollment of 20 patients/year until the required patient number has been reached. 2008: completion of the trial; presentation and publication of final results.

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). At the time of this writing 10k SFr is left over, earmarked for compensation of local trial administration of participating centers.

Treatment with pulse therapy cyclophosphamide is reimbursed by health insurance companies in most participating centers. Reimbursement of extra costs related to the transplantation procedure (e.g. CD34-selection columns, ATG), amounting to EURO 10,000 per patient, is presently arranged on a local level.

Budget
No funding is yet available for trial-related medical expenses nor for trial administrative costs, and budgetary constraints impede implementation of the protocol in several centers and countries.

To ensure continuation of the trial a financial injection of 50k EURO is deemed necessary based on the following estimates:

A. Enrollment of patients.
Promotional activities (newsletter, flyers, website)…….. 3k
Study Administration Office……………………………… 15k
Compensation for local trial administration (1k/pt)…… 10k*
Contribution to medical expenses of transplantation (2k/pt) 10k**

C. Data collection and analysis.
Data monitoring………………………………………….. 5k
Data entry support…………………………………. …….. 5k
Statistical support and interim analyses…………………. 2k

* based on next cohort of 20 patients
**based on next 10 transplant patients
**Organisation**

The trial is conducted by the Scleroderma Study Group of the EBMT/EULAR Working Party Autoimmune Diseases (currently chaired by R. Saccardi). 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 Basel. 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) conducts interim analyses after 20, 40, 60 and 80 patients have been enrolled. The first interim analysis focussed on safety, but upcoming interim analyses will also encompass evaluation of efficacy parameters.

The reports arising from these analyses are reviewed by three independent experts (D Furst, USA, F Wollheim, Sweden, J Apperley, UK), who advise the Study Chairpersons on the conduct of the study. Concise versions of the reports are then provided to participating centers.

The protocol is active in the following centers (local study investigator):

**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-Reynaud), Hopital Claude Huriez, Lille (Prof. Hachulla), 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),

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

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

**Slovak Republic:**
Research Institute of Rheumatic Diseases, Piestany (Prof. Rovensky),

**Switzerland:**
Felix Platter-Spital Basel, Insel Spital Bern (Prof. Tyndall, 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), Groningen University Medical Center (Dr. Bootsma)

**United Kingdom:**
Leeds General Infirmary, Leeds (Prof. Emery)
Scientific side studies linked to the ASTIS trial are conducted 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. If funded by EULAR, EULAR will undoubtedly benefit from positive publicity that will arise from its association with ASTIS, being the first investigator-driven European randomized clinical trial in scleroderma.