European Science Foundation

Standing Committee for the European Medical Research Councils (EMRC)

ESF/EMRC EXPLORATORY WORKSHOP ON:

Graves' Ophthalmopathy

Amsterdam, The Netherlands

18-20 May 2001

Convened by: W.M. Wiersinga

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1. EXECUTIVE SUMMARY

Graves' ophthalmopathy or orbitopathy (GO) is the eye condition observed in patients with Graves' disease, an autoimmune disease resulting in hyperthyroidism. Although eye signs and symptoms develop in about 30-50% of all patients with Graves' disease, more severe ophthalmopathy occurs in 5-15%. GO is always disfiguring (swollen eye lids, protruding eyes) and often invalidating (double vision, corneal lesions, sight loss), resulting in a considerable decrease of quality of life. GO is one of the remaining enigmas in the field of thyroid disease: its pathogenesis remains obscure and its treatment is difficult and not always successful. Due to the relative low prevalence of the more severe forms of GO, few physicians have ample experience with the management of GO patients, and few centers see enough patients to do clinical trials in order to test new treatment modalities. Close cooperation between orbital surgeons and ophthalmologists improves therapeutic outcome, but again such a cooperation is available in only a few centers - experienced orbital surgeons are a rare commodity.

To advance the care of GO patients the initiative was taken to establish an European Group on Graves' Orbitopathy (acronym EUGOGO). Participation was by invitation, based on criteria that centers should be of solid scientific reputation, had vast experience with GO patients and already had established collaborative teams of orbital surgeons and endocrinologists. Nine centers from six European countries compose EUGOGO: Amsterdam and Utrecht in the Netherlands, Newcastle-upon-Tyne and Cardiff in the UK, Mainz and Marburg in Germany, Lyon in France, Pisa in Italy, and Thessaloniki in Greece. The present ESF exploratory workshop was aimed to delineate more precisely the very goals of EUGOGO, to discuss the results of a first multi-center pilot study, and to evaluate the future direction of EUGOGO in terms of financing, the set-up of an European register of GO patients and the feasibility of clinical trials.

It was unanimously agreed that the prime goal of EUGOGO is to establish a European collaboration to enable large multicenter controlled clinical trials to improve the management of Graves' ophthalmopathy, leading to a better quality of life of patients with this chronic and disabling disease. As a first step to reach this goal, one need consensus on standardized and validated assessment methods. To this end a pilot study was done by EUGOGO participants on the appropriateness of a specifically designed case record form (CRF). The pilot study comprised CRF's of 152 newly referred patients collected over a three to four months period (one of the largest series of GO patients assembled so far), and the results were evaluated in depth at the Workshop. Variation between centers in general patient characteristics and in severity and activity of the eye disease was small. Larger variation existed in the methods used for assessing severity and activity of GO, and even more so in the choice of treatment for individual patients. Most importantly it was obvious that the preliminary CRF was too extensive: to fill it out completely was too laborious and very time consuming. Detailed recommendations were put forward to simplify the CRF and to standardize assessment of eye changes. Task groups were created with specific goals : 1) to revise the CRF, 2) to translate the quality-of-life questionnaire specific for GO (the so-called GO-QOL) into French, Italian, German and Greek language, 3) to realize central evaluation of orbital MRI scans, 4) to

propose a study design for the first randomized clinical trial. The task groups will report in writing before the next EUGOGO conference planned in january/february 2002 in Newcastle-upon-Tyne. It is foreseen that during that meeting EUGOGO participants will assess eye changes of a few real GO patients independent of each other: this procedure will enhance further standardization of assessing eye changes, and reduce inter-observer variation. A small second pilot study with the revised CRF might also be evaluated at that meeting.
Other objectives of EUGOGO could be to conduct studies on surgical management, to do basic research studies, and to set up a European register of GO patients. No consensus existed on these secondary goals; three task groups will report on the feasibility of the secondary goals.

The future of EUGOGO is unsafe without external funding. Financial support for a scientific network might be obtained from ESF (with a maximum of 3 years). It was decided to submit a grant application at the European Union (deadline 15 October 2001). Industry up to now is not very interested. Other granting bodies (like charities, scientific societies, patient associations) will also be approached, but income frome these sources will be, if any at all, very limited. Apart from the finances, it looks that EUGOGO can start with the first controlled trials in autumn 2002. Another EUGOGO meeting is consequently scheduled for september 2002 in Thessaloniki.

2. FINAL PROGRAM

Friday 18 May 2001

19.00-19.10	**Welcome address** *Prof. dr. W.M. Wiersinga, Convenor*
19.10-19.40	**ESF/EMRC presentation** *Dr. M. Minkowski, ESF Senior Scientific Secretary*
19.40-20.40	**Goals of EUGOGO**
20.40-21.00	*Break*
21.00-22.00	**Financing of EUGOGO**

Saturday 19 May 2001

EVALUATION OF RESULTS OF THE FIRST PILOT STUDY DONE BY THE PARTICIPATING CENTERS OF EUGOGO

09.00-09.30	**Assessment of general patient characteristics**
09.30-10.00	**Assessment of thyroid state**
10.00-11.00	**Assessment of disease severity** (soft tissue involvement, proptosis, eye muscle motility, diplopia, corneal involvement, optic nerve involvement)
11.00-11.15	*Coffee break*
11.15-12.00	**Assessment of disease activity**
12.00-13.00	**Establishment of consensus on how to assess disease severity and disease activity**
13.00-14.00	*Lunch*

Saturday 19 May 2001 *(continued)*

14.00-14.30	**Assessment of orbital imaging procedures and establishement of consensus**

14.30-15.00	**Assessment of treatment plans and establishment of consensus**
15.00-15.30	**Final delineation of Case Record Form (CRF)**
15.30-16.00	**Plans on meassurement of Quality-of-Life**
16.00-16.15	*Tea break*
16.15-17.00	**Discussion of grant application at the European Union**
17.00-18.00	**Plans for future trials: discussion**

Sunday 20 May 2001

08.30-10.00	**Possibility for other grants**
10.00-10.30	**Cooperation with other scientists in Europe in the field of thyroidology and ophthalmology**
10.30-11.00	**Cooperation with patient associations on thyroid diseases in Europe**
11.00-11.15	*Coffee break*
11.15-12.00	**Remaining issues**

3. SCIENTIFIC CONTENT OF THE EVENT

The major scientific content of the meeting has been the thorough evaluation of the results of a pilot study executed by all participating centers of EUGOGO. The aim of the pilot study was to test the appropriateness and feasibility of a preliminary case-record-form (CRF) of GO patients. The pilot study also would give insights in variation between centers with regard to severity and activity of the eye disease in referred patients. Both the availability of validated CRF's and inventarisation of case mix between centers are absolute requirements for the realistic design of any multicenter clinical trial in the future.

The pilot study comprised CRF's of 152 newly referred patients to the participating centers, collected over a three to four months period. It is one of the largest series of GO patients assembled so far. Variation between centers in general characteristics of GO patients and in severity and activity of the eye disease was small. Larger variation existed in the methods used for assessing severity and activity of GO, and even more so in the choice of treatment for individual patients. Most importantly, it was obvious that the preliminary CRF was too extensive: to fill in the CRF completely was too laborious and very time consuming.

Detailed recommendations were put forward to simplify the CRF and to standardize assessment of severity and activity of GO. This will allow to design a definitive CRF to be used in future clinical trials. A detailed report on the quantitative results of the pilot study, and on the discussion-based recommendations how to improve the preliminary CRF is enclosed. Two scientific papers will be submitted for publication in peer-reviewed journals: one on the assessment of GO including a colour atlas of the grading of eye changes by J. Dickinson and her collegues from Newcastle-upon-Tyne, and one on the results of the pilot study on behalf of EUGOGO.

4. LIST OF PARTICIPANTS

CONVENOR
Prof. dr. Wilmar M. Wiersinga

EUROPEAN SCIENCE FOUNDATION
Dr. M. Minkowski

ORBITAL SURGEONS
- Dr. L. Baldeschi
- Dr. A.J. Dickinson
- Dr. A. Halkias
- Dr. G. Heufelder
- Dr. R. Kallmann
- Mrs. C. Lane
- Prof. dr. M. Nardi

ENDOCRINOLOGISTS
- Prof. dr. A.E. Heufelder
- Prof. dr. G. Kahaly
- Prof. dr. P. Kendall Taylor
- Prof. dr. G.E. Krassas
- Prof. dr. C. Marcocci
- Dr. M.F. Prummel
- Dr. R. Rocchi

MEDICAL INFORMATICS
Dra. Annemieke Bakker

APOLOGIES
- Prof. dr. A. Hullo
- Prof. Dr. J.H. Lazarus
- Dr. M.Ph. Mourits
- Prof. dr. J. Orgiazzi
- Dr. P. Perros
- Prof. dr. A. Pinchera
- Dr. S. Pitz