

Clinical Studies Group Strategy

A. Clinical Studies Group: Autoimmune Rheumatic Disease

Chair: Professor David Isenberg

Disease/disorders covered:

1. Systemic Lupus Erythematosus
2. Sjögren's Syndrome
3. Polymyositis
4. Vasculitis
5. Antiphospholipid antibody syndrome
6. Scleroderma

Approach used to prioritise between disease areas:

The CSG has developed sub-groups in each of these six areas and consider all studies emerging from them. Prioritisation between disorders is based on tractability of the question and the perceived importance for that disease study group.

B. Disease/Disorder:

Given the sub-division into the six different disease study groups the processes for informing strategy were different between diseases.

SYSTEMIC LUPUS ERYTHEMATOSUS

Sources used to inform strategy

a) Consultations with stakeholders

The British Isles Lupus Group (BILAG) was established in 1984 and has met regularly about three times a year ever since. This group now consists of 15 ('Lupologists') from all over the UK and has a broad range of interests in clinical aspects of lupus, its pathogenesis, optimising its assessment and developing new ideas for treatment. Professor Caroline Gordon represents the interests of lupus research on the sub-committee and undertook detailed discussions with other BILAG group members and with those attending the lupus special interest group at the annual BSR meeting.

b) Review of published and other evidence (e.g. databases)

Although the questions formulated by the group to date, have not been subject to formal

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review of publications, the BILAG group members are all highly knowledgeable about the subject and well informed about manuscripts relevant to the discussions which have taken place. For those topics selected as priorities the CSG has considered both published trials as well as searching data sources of registered ongoing trials being conducted with funding from **arc** and other UK bodies. Such formal reviews have not yet initiated of published evidence, but with the appointment of Diane Roberts as **arc** CSG Information Officer we have plans to do so.

c) Identification of emerging technologies

Not relevant.

Approach used to develop consensus:

Professor Gordon, following discussions with BILAG and other lupus interested "parties" (see above), proposed four broad topics to the CSG sub-Committee. These were discussed in detail (the minutes of the relevant meetings are on the CSG website: http://www.arc-research.org.uk/med_director/autoimmcsq.asp) and there has been an exchange of views between the BILAG group and the CSG sub-committee before concluding that one topic (see section C.1.) was most worthy of pursuing at this time.

SJOGREN'S SYNDROME

Sources used to inform strategy

a) Consultations with stakeholders

Dr Simon Bowman who represents the interests of Sjögren's syndrome on the Sub-Committee, consulted widely with members of the British Sjögren's group which meets on an ad hoc basis and those who attend the Sjögren's special interest group at the BSR.

b) Review of published and other evidence (e.g. databases)

As with the Lupus Group, rather than utilising any formal review of published evidence, the collective interests of those expert in Sjögren's, all very well informed individuals, were asked to determine if there are particular needs for this group of patients. We envisage making use of Diana Roberts (**arc** Information Officer) to obtain a full literature review in the future.

c) Identification of emerging technologies

One application which has emerged involves an 'intra-oral electronic stimulator' to stimulate those remaining labial glands in the mouth in the hope of improving the severe dryness of the oral cavity that forms such an important part of this condition.

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Approach used to develop consensus:

To develop consensus, Dr Bowman presented various potential ideas to the **arc** sub-committee, took the advice given back to his stakeholders and has focused principally on two projects which have been developed (see section C.2.)

INFLAMMATORY MUSCLE DISEASE

Sources used to inform strategy

a) Consultations with stakeholders

This group has not yet fully established its working methods for seeking priorities. The number of physicians with an interest in myositis in the UK is small, well networked and are fully represented on the CSG.

b) Review of published and other evidence (e.g. databases)

The Myositis sub-group has not formally reviewed the published evidence although the expertise on the CSG coupled with the well known paucity of published clinical trials in this area does not make this a significant task. We envisage making use of Diana Roberts (**arc** Information Officer) to obtain a formal literature review including ascertaining knowledge on ongoing registered trials.

c) Identification of emerging technologies

Not relevant.

Approach used to develop consensus:

As a formal strategy for myositis is still under development the CSG supported a proposal by Professor Michael Hanna, Consultant Neurologist, Queen Square for **arc** involvement in a study on inclusion body myositis, a disorder for which there is no proven effective remedy. It was agreed that with the rarity of inclusion body myositis both this disease and the drug proposed to be used in this treatment, arimoclomol, was appropriate (see section C.3.).

VASCULITIS

Sources used to inform strategy

a) Consultations with stakeholders

The CSG sub-group on vasculitis strategy is primarily informed by the wider discussions within The British UK Vasculitis Group. This has met on a regular basis and there is a Vasculitis Special Interest Group at the BSR. The group has been tasked with providing a priority listing to the CSG and are represented on the Committee by David Jayne.

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b) Review of published and other evidence (e.g. databases)

While no formal review of published data has taken place, Dr Jayne and his colleagues are widely read and highly knowledgeable. They are well aware of the literature on all aspects of Vasculitis. We envisage making use of Diana Roberts (**arc** Information Officer) to obtain a formal literature review including ascertaining knowledge on ongoing registered trials.

c) Identification of emerging technologies

Not relevant.

Approach used to develop consensus:

Discussions are ongoing on which of the several potential projects they are going to support (see section C.4). Consultations have taken place, both between members of the vasculitis group itself and between David Jayne and members of the CSG. The aim is to achieve consensus within the next few months. The emerging priorities will then be publicised via the **arc** website for external comment.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Sources used to inform strategy

a) Consultations with stakeholders

At this stage there has been no formal consultation process or meeting with interested priorities though such a forum, hopefully face to face is planned for 2009. There have been informal discussions between David D'Cruz, the sub-group leader and the small group of physicians with a well known interest.

b) Review of published and other evidence (e.g. databases)

There has been no formal review of the evidence by Dr D'Cruz and colleagues but they are all intimately aware of the challenges faced by this difficult condition and are fully *au fait* with the key references in this area. We envisage making use of Diana Roberts (**arc** Information Officer) to obtain a formal literature review including ascertaining knowledge on ongoing registered trials.

SCLERODERMA

Sources used to inform strategy

a) Consultations with stakeholders

Christopher Denton represents the interests of scleroderma on the **arc** sub-committee.

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His views are informed by discussions with the UK Scleroderma group which is long established, as an open group who meet on a regular basis and also in the context of the BSR Special Interest Group. The UK group have been tasked by Professor Denton to come up with priorities for clinical trials.

b) Review of published and other evidence (e.g. databases)

Although not formally reviewing the evidence, Professor Denton and his colleagues are very well aware of all the relevant and main publications in the field of Scleroderma. We envisage making use of Diana Roberts (**arc** Information Officer) to obtain a formal literature review including ascertaining knowledge on ongoing registered trials.

Approach used to develop consensus:

The scleroderma group was approached by Dr Redmond at Leeds with a simple proposal to assess the value of improving the outcome of foot care in patients with scleroderma. It has been agreed by the interested parties that this problem is an area of real need in scleroderma.

C. Emerging Therapeutic and Related Areas

C.1. SLE Therapeutic Area: CNS Lupus

1. B cell depletion and the treatment of lupus affecting the central nervous system
2. Optimising the use of ACE inhibitors in renal lupus
3. The establishment of a bio-bank in patients with SLE
4. Evaluating the sensitivity to change of a lupus specific quality of life index

The CSG then considered the justification for these four areas and decided to prioritize the CNS lupus issue. It was felt that the establishment of a bio-bank for lupus patients while potentially useful, without the development of a question or a series of questions was inappropriate for the new clinical trial schemes.

The use of ACE inhibitors whilst of interest in renal disease may not be a really major issue and since so many patients with lupus are receiving this drug anyway, it would be hard to perform a study.

Quality of life assessment is relevant and we are exploring the possibility of extending the work undertaken by Lee Suan Teh by assessing the sensitivity to change of a lupus specific quality of life index. This will, we hope, be ready to send to **arc** next year.

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a. Proposed study question

- What is the role of B cell depletion using rituximab in the treatment of patients with lupus involving central nervous system?

b. Justification for question

CNS lupus remains a complication of lupus that is often distressing for the patient and difficult to control with conventional immunosuppressive therapy. There are few industry sponsored clinical trials in patients with lupus and the potential complexity of some of the clinical features has led to the exclusion of active CNS problems from these trials. The success of B cell depletion in reducing disease activity in lupus 'generally' suggests it is appropriate to try this agent in CNS lupus and some small open label studies have reported encouraging results.

C.2. Sjögren's Syndrome

1. Use of B cell depletion using rituximab in the treatment of Sjögren's Syndrome
2. The use of artificial stimulation to the labial glands to increase the yield of saliva

a. Proposed study question(s)

- What is the role of rituximab in the treatment of patients with Sjögren's Syndrome?

b. Justification for selection of question

The Sjögren's group have decided to go forward with the principle study of using rituximab in the treatment of Sjögren's syndrome. This study is timely as it makes use of some newly developed tools (developed by the British Sjögren's group) to assess the activity and damage evident in patients with Sjögren's syndrome and the fact that some small open studies have indicated this approach is feasible and may be beneficial.

a. Proposed study question(s)

- To assess the potential value of a form of oral electronic stimulation of the labial glands in patients with Sjögren's

b. Justification for question

Keeping the buccal cavity moist is a key therapeutic goal for both patients and physicians. This non-pharmacological approach requires formally testing for its feasibility, acceptability and its impact on quality of life. This study is still being developed and it is hoped that it will be submitted later in 2009.

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C.3. Myositis

a. Proposed Study question

- Is there any preliminary evidence that aricimoclomol is effective in patients with inclusion body myositis?

b. Justification for selection of question(s)

Whereas immunosuppressive drugs (and more recently, rituximab) have been shown to be of some value in small open label studies of patients with myositis (there is a major ongoing study of rituximab principally taking place in the United States at the moment), these studies invariably exclude inclusion of body myositis for which no satisfactory conventional immunosuppressive therapy treatments have emerged. There are reasonable reasons to believe that aricimoclomol may well be worth pursuing in the treatment of inclusion body myositis. Furthermore, the study is timely as the 'MITAX' disease activity assessment tool and the 'MYODAM' disease damage tool have now been validated and shown to be sensitive to change.

C.4. Vasculitis

At this stage, amongst a broad range of possible studies, the use of TNF alpha blocking agents in Takayasu's arteritis has been considered, as well as new therapeutic agents in the several conditions and optimising the use of immunosuppressive treatment in patients with polymyalgia rheumatic or giant cell arthritis.