Editorial

The origins, evolution and future of the International Myositis Assessment and Clinical Studies Group (IMACS)

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IMACS: in the beginning

Peter Medawar, Professor of Zoology at University College London and Nobel Laureate, observed that 'isolation in science is over, we all depend upon and sustain one another'. This observation can certainly be extended to clinical medicine, perhaps nowhere better than to the plethora of international rheumatology disease-focused groups that have formed dynamic working partnerships aimed at achieving collaborative endeavours, devising validated outcome measures, performing multicentre clinical trials, and working with basic scientists to study the origins of each condition.

The International Myositis Assessment and Clinical Studies group (IMACS) was formed following an impromptu meeting held in 1999 at the hotel bar adjacent to Glasgow's exhibition centre, where a European League Against Rheumatism (EULAR) meeting was held. Professor David Scott (King's College London, UK) invited several individuals known to be interested in inflammatory muscle disease, including some of the authors of this article (David Isenberg, Fred Miller, Lisa Rider), together with Drs. Lori Love, Jiri Vencovsky, Ingrid Lundberg, Katalin Danko, and Chet Oddis. At that initial meeting, it became clear that those present were willing, and indeed eager, to work together. Names, addresses, and telephone numbers were exchanged [little email in those days!]. The group met soon after in Oxford, UK, along with patient representatives from Myositis UK, and established concepts of disease activity, disease damage and patient reported outcomes. Disease activity was defined as reversible inflammatory components of disease, and disease damage as cumulative, often irreversible changes that result from previously active disease, treatment and/or other concomitant disorders. The group also reviewed and established core set measures for disease activity and damage for all forms of myositis in adults and children (1). A broad agreement was achieved that the group could provide a valuable service by developing a "user-friendly" disease activity tool and a damage index (2).

IMACS expanded to a coalition of health care providers and researchers with experience and interest in the myositis syndromes and evolved to become more inclusive, growing initially to about 50-75 members, including paediatric and adult specialists (Fig. 1).

Development of disease activity and damage assessment tools

David Isenberg encouraged the development of the MITAX (Myositis Intention to Treat Activity indeX) being based on the principle of the 'physician's intention to treat' principle. This principle had been used in the development of British Isles Lupus Assessment Group (BILAG) Index (3) to capture disease activity in patients with lupus. This was complimented by a series of visual analogue scales capturing activity in the various organs and systems affected in patients with inflammatory muscle disease, notably the constitutional, articular, cardiopulmonary, gastrointestinal, cutaneous and musculoskeletal systems. These series of scales form the Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT) component of the disease activity index. The Myositis Disease Activity Assessment Tool has filled an important void, as global activity, muscle strength, physical function and enzymes had all been partially validated core set activity measures, but an extramuscular assessment tool was lacking (2).

The activity indices were evaluated in real patient exercises organised in Lon-

Fig. 1. An early IMACS meeting, the International Workshop on Myositis Outcome Measures and Clinical Trial Design Issues, held in New Orleans, LA, USA on October 22-23, 2002.
Many of the members in attendance were part of the original group of researchers who joined IMACS. The group developed consensus on the degree of clinically important change in core set activity measures (2), consensus Preliminary Definitions of Improvement as the initial response criteria for adult and juvenile dermatomyositis and polymyositis (14); consensus on clinical trial design issues (15); and finalised the content of the Myositis Damage Index (9, 10).

don in March 2001 and May 2002. The key messages from these early studies were that the MITAX and MYOACT systems worked well, although disease activity in the musculoskeletal system exhibited relatively poor reliability and physician agreement (4). Subsequently the tools were modified; Shabina Sultan undertook substantial reliability studies involving more than 100 patients at seven centres in Europe and the United States by comparing her assessments with those of the local physician, which resulted in additional improvements (5).

The key principle of the MITAX (and BILAG) system is that they provide a testable hypothesis, based on the linking of activity categories to the change in therapy. The criteria and validity of the "A" (most active) score in the individual organ or system on MITAX was determined by two large multi-centre studies, again led by Shabina Sultan (4). There was generally good reliability on the MITAX, with an inter-rater correlation coefficient of greater than 0.65 in most systems, and good convergent validity between MITAX and MYOACT. The Myositis Disease Activity Assessment Tool has gone on to be used by investigators in clinical and translational studies, and as a core set measure of extramuscular activity in therapeutic trials (6-8).

A Myositis Damage Index (MDI) was simultaneously developed as a modification of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Lupus Damage Index (3). It distinguishes damage in 11 organs or systems using a very simple nominal scale. Its purpose was not intended to ascertain the precise cause of the damage, but to identify organ system damage that developed after the diagnosis of myositis. Linked to this, we developed the Myositis Disease Damage Assessment Tool (MYODAM) – a series of 10 cm visual analogue scales used to quantitate the severity of the damage. Several multi-centre studies established good interrater reliability, excellent convergent validity between the MDI and the MYODAM, good construct validity with other damage measures, and excellent predictive validity with correlations of MDI scores with disease course and even mortality in adult and juvenile DM and PM patients (9, 10). The validated Myositis Damage Index inspired natural history studies to better examine and compare long-term outcomes in myositis populations throughout the world (11-13).

Response criteria and other IMACS research projects

Following the initial development and validation of core assessment tools, IMACS established its goals more broadly to include improving the lives of children and adults who suffer from myositis. By enhancing collaborations, IMACS fostered discovery of better therapies, as researchers and clinicians gained improved understanding of mechanisms of disease and of how to best assess and treat these conditions. IMACS members have worked to achieve these goals by developing and validating these and other assessment tools as core set measures of disease activity and damage. IMACS developed an initial responder index for juvenile and adult dermatomyositis and polymyositis for use in clinical trials, known as the Definitions of Improvement (14) based on limited natural history and clinical trial data and relying on group consensus, as well as consensus standards for the conduct and reporting of adult and juvenile myositis studies (15). IMACS members performed collaborative therapeutic trials, notably the international multi-centre trial of rituximab for adult and juvenile dermatomyositis and polymyositis (7), among others. After the accumulation of adequate randomised controlled

therapeutic trial and natural history data, IMACS members then developed fully validated response criteria for juvenile and adult dermatomyositis and adult polymyositis that define minimal, moderate and major clinical response and appear to be more sensitive in detecting clinical improvement. The new criteria are hybrid criteria consisting of a conjoint analysis model based on the absolute change of the IMACS core set activity measures, which are differentially weighted (or utilising The Paediatric Rheumatology INternational Trials Organisation (PRINTO) core set measures) (16-18). These new criteria have been endorsed by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR), and are now being widely used in therapeutic trials. The IMACS website hosts web-calculators for these criteria to facilitate their use (https://www.niehs.nih.gov/research/resources/imacs/response_criteria/index.cfm).

IMACS has subsequently planned and conducted international collaborative myositis research. For logistic and cost reasons, the administrative arm of IMACS has been housed in offices of the National Institute of Environmental Health Sciences (NIEHS) in the Mark O. Hatfield Clinical Research Center at the National Institutes of Health, Bethesda, Maryland, USA. IMACS has undertaken several research projects consistent with its goals that have resulted in numerous advances and publications (see https://www.niehs.nih.gov/research/resources/imacs/imacspubs/index.cfm). IMACS members contributed to the development of new classification criteria for patients with myositis (19), which are based on a probability score model, inclusion of broad clinical and muscle biopsy features, and have the ability to subclassify a number of clinical subgroups. These new classification criteria have also been endorsed by the ACR and EULAR, and are now widely used in clinical studies.

Other completed projects have involved a broad range of important clinical issues in myositis: understanding dyslipidemia in myositis (20); development of a core set of tests to assess fitness and strength in patients with myositis (21); understanding therapeutic decisions towards developing standardisation in treatment regimens (22); development of an internationally agreed core dataset for juvenile dermatomyositis for clinical and research use (23); guidelines for cancer screening and follow-up of myositis phenotypes (24); perceptions and pitfalls in myositis autoantibody assays (25); and calcinosis biomarkers in dermatomyositis (26). Members continue to work in other important areas, including screening, treatment, and follow-up of myositis-associated interstitial lung disease; development of validated patient-reported outcomes (in collaboration with OMERACT); development of validated measures to assess disease in patients with inclusion body myositis (IBM); and achieving a better understanding of the genetics of myositis and the major phenotypes, among other areas. This work has not only helped to advance the standardisation of conduct of clinical and therapeutic studies, but also enabled better definition of myositis subtypes, now defined according to myositis-specific autoantibodies that were previously described by IMACS collaborators and now available for commercial testing.

Enhancing scientific collaborations and advances and mentoring future myologists

Accomplishing these goals has required the contribution and collaboration of multiple investigators, and the formation of several committees, including a Scientific Committee to provide peer-review to strengthen and approve proposed IMACS projects, and a Meeting Committee to plan and operate the annual meetings. More recently, scientific interest groups have been formed to facilitate debate and progress on major unresolved issues in the field of myositis, and to accommodate the growing range of interests that has blossomed from an initial handful of investigators to the now over 600 members representing many clinical adult and paediatric specialties and scientific disciplines, from academia, industry, and non-profit organisations, and including patient representatives. Additionally, IMACS has sponsored meetings around the world to achieve consensus on these issues using nominal group and Delphi techniques. Training in the use of the assessment tools and outcome measures has also been an important element of IMACS, and a variety of materials are now available on its website, including a certificate training programme for members. A registry of myositis subjects' clinical and outcome data has been used to develop the outcome measures and is now available for members' studies, after obtaining appropriate approvals.

Responding to concerns from trainees and others about the relative lack of opportunities for interactions with senior myositis researchers, and to allow development and nurturing of the next generation of myologists, IMACS created a mentorship programme. The IMACS Mentorship Programme provides the platform to connect early-career myositis researchers and clinicians with mentors that are established in the field to facilitate career development and to encourage continuing contributions in support of improved understanding of myositis and myositis treatment options. Mentors and mentees are strongly encouraged to meet two to four times a year in person and/or by phone to work together on career development and projects over a two-year period.

IMACS has achieved recognition for its multidisciplinary and international collaborative efforts and accomplishments in receiving the 2019 Global Genes Rare Champion of Hope Award for Research Collaboration.

The future of IMACS

The field of myositis has come a long way since the inception of IMACS. It is vital in such a rare disease to combine forces globally, we are stronger collectively than individually and this is where IMACS will continue to help foster innovations in myositis. As IMACS has grown and myositis disease understanding advanced, neurologists, pulmonologists, dermatologists, rehabilitative healthcare providers, geneticists and others joined the group. This has led to the progressive expansion of the multidisciplinary membership of IMACS to the current size of about 650 members who originate from nearly 50

Fig. 2. The 2nd Global Conference on Myositis held in Potomac, MD, USA, on May 5-8, 2017, organised by Dr. Frederick Miller. The conference was attended by nearly 300 participants from 5 continents, many of whom are members of IMACS.

countries across the globe (Supplementary Fig. S1 and Table S1).

IMACS also provides a vital global network bringing together collaborative groups with common interests and helps to bridge medical sub-specialities. A bulletin board will soon be available on the IMACS website to facilitate keeping members in better touch with the international myositis community. The field of IBM remains a challenge where no current disease-modifiable treatments are available; ongoing efforts between rheumatology and neurology within IMACS remain vital in achieving this objective. The number of IMACS registered Scientific Interest Groups has continued to grow with the recent creation of the dynamic IBM group and the addition of the Myositis Genetics Consortium (MYOGEN), as well as formation of a group dedicated to telemedicine in myositis, which formed since the COVID-19 pandemic. These new scientific interest groups are leading additional novel projects and collaborations. IMACS efforts will likely lead to an increase in multicentre therapeutic trials of new targeted therapies and large studies combining myositis-specific serology, genetics, and identified risk/protective environmental factors, which may assist future screening and preventive strategies.

IMACS is also interfacing with and facilitating other important global initiatives within the field of myositis. Crosstalk amongst various specialties with overlapping interests in myositis was the catalyst for the first Global Conference on Myositis (GCOM) in Stockholm in May of 2015 that Professor Ingrid Lundberg organised. This evolved into bi-annual events in Potomac, MD (Fig. 2), followed by Berlin. At the 3rd GCOM meeting in March of 2019, the International Myositis Society (iMyoS) was created, with the support of the IMACS membership. It is with the opening of iMyoS that IMACS will partner on translating many of its research achievements to the endeavours of iMyoS, who will lead the education of myositis specialists throughout the world by promoting curricula and fellowship programmes and striving to implement interdisciplinary standards of care on a global scale.

IMACS will continue to adopt a global and inclusive approach to maintain the collegial way that myositis collaborators work together without geographic boundaries and to collaborate with synergistic myositis-focused groups. On this inauguration issue of *Clinical and Experimental Rheumatology* dedicated to myositis, led by iMyoS, we look forward to a future of myositis research and education in partnership, together.

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