Dando Fellowship - Evaluation of the clinical, microvascular imaging and serum biomarker response to antithrombotic agents in Raynaud's phenomenon and scleroderma-spectrum disorders

Summary of scope of RSA fellowship

The principle objective of the research we are undertaking as part of the Dando fellowship is to establish a 'proof of concept' for the potential therapeutic benefits of asasantin retard (combination aspirin and dipyridamole) in the management of Raynaud's phenomenon, particularly in the context of systemic sclerosis. Our study will contribute to our understanding of the role of platelets in the pathogenesis of scleroderma spectrum disease and is an important, and necessary, "first step" before contemplating larger studies designed to assess the safety and efficacy of long term treatment with asasantin retard in patients with scleroderma. Since requesting funding we have significantly extended the scope of the original protocol including evaluation of platelet function and oxidative stress to maximise the scientific quality of the work. This study has also allowed us to evaluate the potential clinical applications of a novel non-invasive microvascular imaging technique (laser contrast speckle imaging). The research undertaken as part of this fellowship shall form the main body of a thesis submitted to the University of Bath as part of a Doctorate of Philosophy (PhD).

The fellowship has allowed me to develop specialist expertise in the diagnosis and management of Raynaud's phenomenon and scleroderma spectrum disorders, beyond that typically acquired as part of standard Rheumatology specialist training. Development of a specialist Raynaud's and scleroderma service and implementation of a new echo service will ensure a continued legacy of the Dando fellowship that shall improve the provision of care for existing and new patients with Raynaud's and scleroderma.

Changes to the service provision at RNHRD

Patients with Raynaud's and scleroderma were previously seen as part of a connective tissue disease service. The development of a dedicated Raynaud's and scleroderma service undertaken by myself in conjunction with Sister Sue Brown (under the supervision of Professor McHugh) has allowed us to streamline our service further, ensuring comprehensive assessment of all organ systems in addition to specialist counselling and education for patients. This service allows the systematic collection of health outcome measures recommended as part of good clinical practice and is also important for future research into scleroderma spectrum disease. The clinic runs on a monthly basis but as demand rises, we anticipate increasing the frequency of the service to every fortnight in the future. The success of this new service is not dependent on RSA support and will continue beyond the duration of the Dando fellowship.

I recently audited the frequency of cardiopulmonary investigation in patients with scleroderma against national guidelines. We identified an important deficiency in echocardiographic screening for latent pulmonary vascular complications. To this end, I have helped facilitate the development of a new echocardiography service at RNHRD to coincide with the scleroderma clinic. This should promote earlier detection of cardiopulmonary disease whilst also enhancing the patient journey by reducing the frequency of hospital attendances for subsequent investigations.

Regulatory approval

No studies undertaken in humans, or necessitating review of medical records, can be undertaken without necessary regulatory body approval. This has been the first time that I have completed such applications to regulatory bodies and has taught me a huge amount about research governance and the regulatory protection of subjects entering into clinical trials.

I have requested regulatory approval for 2 main studies. For the healthy control study we first had to receive approval from the local ethics committee (Bath REC) and the RNHRD Research & Development (R&D) committee. This study has subsequently been completed (see later).

Phase 2 of my research involves use of an interventional medicinal product (asasantin retard) and as such necessitates additional approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Human Tissue Authority (HTA). The process of obtaining regulatory approval is a major component of any research project and takes a significant amount of time. Having received approval to proceed with the interventional study back in January (from Bath REC), we were surprised to have been recently informed by the National Research Ethics Service (NRES) that Bath REC did not have the authority to grant such an approval. NRES have been clear that this was not an oversight that we could have prevented and an investigation is underway to ascertain how such a breach in protocol could have happened. This unexpected announcement has delayed recruitment to this study as we have been forced to reapply to another committee. Thankfully, a fresh application to a new REC has now been completed and received the necessary approval, and we are once again in a position to proceed with the study.

Data collection to date

A major component of the research is the validation of a novel non-invasive microvascular imaging assessment tool (laser contrast speckle imaging, LCSI). The current gold standard for dynamic assessment of digital microvascular function is infrared thermography (IRT). To understand the potential clinical application of LCSI in the assessment of Raynaud's and Scleroderma, it is important to first explore the strengths and limitations of comparator techniques such as thermography. To this end, we have undertaken a large retrospective review of all patients with Raynaud's and/or systemic sclerosis who have attended for thermography at the Royal National Hospital for Rheumatic Disease (RNHRD) over the last 10 years. In parallel, we first recruited as many such patients as possible to our scleroderma database (that now numbers approximately 250 patients with SSc who have given full consent for our research studies). We are in the process of writing this work up.

We have also completed recruitment, data collection and analysis of a prospective healthy control study comparing IRT and LCSI which forms a major part of the validation of the new imaging technique. I am currently writing this work up and will submit it for publication shortly. It shall also form a chapter of my PhD thesis.

As already discussed, we are now in a position to begin the interventional study that shall form the main body of the research and hope to begin recruitment imminently.

University of Bath Registration

I have registered with the University of Bath and plan to submit my work for a Doctorate of Philosophy (PhD). I have registered my doctorate through the School of Pharmacy and Pharmacology (Grade 5a rated in last RAE). The added benefit of affiliation with such a prestigious department is that it has fostered interest in scleroderma with senior scientists with the department (e.g. Professor Ward and Dr Malcolm Watson are now co-supervisors).

This collaboration has also allowed us to explore aspects of platelet function not included in the original fellowship application. In addition to circulating markers of platelet activation and endothelial dysfunction, we have now incorporated tests specific to platelet function (platelet aggregometry). The unit in Bath have also developed an interest in markers of oxidative stress (isoprostanes) that are highly relevant to scleroderma spectrum disease and the potential therapeutic response to asasantin retard (dipyridamole is a potent antioxidant).

Peer reviewed publications

Regulatory approval, data collection and the publication process prevent rapid translation of research hypotheses into published reports. Nonetheless, we have published extracts from a comprehensive literature review, and are in the process of writing up the findings of the healthy control study and the retrospective review of thermogrpahic images that we hope to publish in the coming months. We also have the results of the aforementioned audit in press. Over the course of the year, I have encountered some interesting cases that have been accepted for publication as case reports (an important means of highlighting to the scientific community rare or unusual presentations of scleroderma spectrum disorders). I have appended these papers for your interest.

Laboratory techniques

I have developed experience in the following laboratory techniques relevant to scleroderma research:

- Infrared thermography
- Laser contrast speckle imaging
- Immunoprecipitation
- Enzyme linked immunoassays
- Light transmission platelet aggregometry
- Nailfold capillaroscopy

I am also developing experience in statistical analysis using SPSS software.

The next 12 months

The primary objective of the next 12 months is recruitment of subjects to our interventional study. I plan to complete writing up work undertaken over the last year. We shall also continue to refine and improve the services offered by the RNHRD to patients with Raynaud's phenomenon and systemic sclerosis.

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