Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Management of systemic sclerosis – better follow up, risk stratification and use of immunosuppression

1. Summary of the impact

Systemic sclerosis (SSc) is an important, but uncommon, connective tissue disease with high mortality and has a major non-lethal morbidity. Research at UCL has been instrumental in defining modern management of SSc and has contributed in three main ways. First we have defined the importance of regular proactive screening of cases, secondly we have defined the use of immunosuppression and thirdly we have delineated important clinical and laboratory subsets of SSc that underpin an individualised (or personalised) approach to assessment and treatment. These topics exemplify stepwise progress in management of SSc that also has direct relevance to other more common medical conditions.

2. Underpinning research

From 1993, under the direction of Carol Black, then from 2006 under Chris Denton and David Abraham, the Centre for Rheumatology and Connective Tissue Diseases at UCL pioneered translational research in scleroderma. We recognised the value of systematic collection of bio-samples and careful cataloguing of longitudinal clinical data related to a unique cohort of patients. Thus we have data spanning 20 years on more than 2,000 cases – the largest single centre cohort in Europe and equal to any in the world. This resource has been used to identify key targets for therapy and define novel pathogenic mechanisms. We were the first to describe altered chemokine expression in SSc and these observations delineated key mechanisms of immunopathogenesis **[1]**.

In addition we have discovered factors that predict future deterioration of skin, lung or other organ-based complications of SSc. These are landmark studies that have been adopted as standard of care across many centres internationally. We have pioneered the use of skin score trajectory as a way of stratifying SSc cases **[2]**. Work led by Denton has enabled more informative recruitment into clinical trials, to make these studies more robust and also to help focus resources and therapies appropriately. In a landmark study we showed that regular screening and a proactive strategy significantly improved survival in diffuse SSc **[3]**. Our work on SSc-specific autoantibodies has used the unique resource of our large cohort of cases to define associations that are durable through the course of disease and permit more individualised risk stratification of SSc cases at diagnosis so that treatment and investigation is targeted more effectively. Our research defined hallmark SSc antibodies associated with lung fibrosis (anti-topoisomerase-1; ATA) and scleroderma renal disease (anti-RNA polymerase-III; ARA) **[4]**.

Our centre conducted the first major prospective controlled study comparing intravenous cyclophosphamide with placebo for lung fibrosis complicating SSc **[5]**. As a result of this research, our treatment protocol using intravenous cyclophosphamide has been adopted by most centres in USA and Europe. Together with the Royal Brompton Hospital, we have helped to define those cases that are at risk of progression and developed and validated a simple data-driven staging system of disease severity **[6]**. This was independently validated by data from a large North American trial, the scleroderma lung study. In a related study we used an observational design to complete one of the largest prospective evaluations of immunosuppression in SSc skin disease, focusing on the more severe diffuse subset of the disease **[7]**. This UK observational study recruited nearly 150 cases of dcSSc, more than half from our centre, and evaluated immunosuppressive therapies including mycophenolate mofetil, cyclophosphamide, methotrexate and anti-thymocyte globulin. This study was a landmark initiative as it demonstrated that protocolised approaches with standardised observation, analogous to oncology strategies, could be used to explore best therapies for SSc, a condition with outcome worse than many

malignancies.

3. References to the research

[1] Denton CP, Abraham DJ. Transforming growth factor-beta and connective tissue growth factor: key cytokines in scleroderma pathogenesis. Curr Opin Rheumatol. 2001 Nov;13(6):505-11. http://www.ncbi.nlm.nih.gov/pubmed/11698729

[2] Shand L, Lunt M, Nihtyanova S, Hoseini M, Silman A, Black CM, Denton CP. Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. Arthritis Rheum. 2007 Jul;56(7):2422-31. http://dx.doi.org/10.1002/art.22721

[3] Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM. 2010 Feb;103(2):109-15. http://dx.doi.org/10.1093/qjmed/hcp174.

[4] Penn H, Howie AJ, Kingdon EJ, Bunn CC, Stratton RJ, Black CM, Burns A, Denton CP. Scleroderma renal crisis: patient characteristics and long-term outcomes. QJM. 2007 Aug;100(8):485-94. http://dx.doi.org/10.1093/qjmed/hcm052

[5] Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, Roberts C, Desai S, Herrick AL, McHugh NJ, Foley NM, Pearson SB, Emery P, Veale DJ, Denton CP, Wells AU, Black CM, du Bois RM. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 2006 Dec;54(12):3962-70. http://dx.doi.org/10.1002/art.22204

[6] Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A, Bozovic G, Denton CP, Black CM, du Bois RM, Wells AU. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008 Jun 1;177(11):1248-54. http://dx.doi.org/10.1164/rccm.200706-877OC

[7] Denton CP, Merkel PA, Furst DE, Khanna D, Emery P, Hsu VM, Silliman N, Streisand J, Powell J, Akesson A, Coppock J, Hoogen F, Herrick A, Mayes MD, Veale D, Haas J, Ledbetter S, Korn JH, Black CM, Seibold JR; Cat-192 Study Group; Scleroderma Clinical Trials Consortium. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. Arthritis Rheum. 2007 Jan;56(1):323-33. http://dx.doi.org/10.1002/art.22289

4. Details of the impact

The last 20 years has seen a significant improvement in outcome for patients with scleroderma, and specifically an increase in survival, much of it attributable to research from our centre. We have more than 2,000 cases, seen over the past 20 years, where we have explored the change in outcome over time and also used the uniquely well-characterised patient cohort to define timing and frequency of each of the major life-threatening complications of the disease. Our SSc cohort saw approximately 20 fewer deaths in 2010 compared to 1994. In addition, by avoiding unnecessary high dose immunosuppression there were 10% fewer hospital admissions for infection 2005-10 compared with 1990) **[a]**.

Defining subsets of SSc to improve treatment

The biomarkers we have described have enabled better prediction of complications such as scleroderma renal crisis and lung fibrosis, and identified subsets that benefit from more aggressive treatment. As a result of our definition of hallmark SSc antibodies associated with lung fibrosis and scleroderma renal disease, these tests are now routinely used in risk assessment of SSc

worldwide. They have been incorporated into new classification criteria for SSc issued by the American College of Rheumatology (ACR) the European League Against Rheumatism (EULAR) in 2013, to which we contributed **[b]**. This permits more effective patient education and earlier engagement with other specialised hospital services.

Defining the use of immunosuppression

We have defined the cases of lung fibrosis in scleroderma that are most likely to benefit from immunosuppression and developed a simple staging system for lung fibrosis that is now used in most centres in UK and abroad and has been validated in two independent studies in the USA **[c]** and Australia. This helps to avoid use of toxic immunosuppression in cases of SSc where this is unnecessary and enables us to target immunosuppressive therapy to more severe cases who gain the most benefit. This is a result of our definition of "good prognosis" cases of SSc. A logical extension of this work is more effective enrichment of clinical trial cohorts to allow smaller sample size and improved study design. Our approach using cyclophosphamide is incorporated into the European recommendations for treatment of SSc **[d]** and is now effectively standard of care for SSc cases worldwide **[e]**.

Defining the importance of regular proactive screening of cases

As a result of our research, regular screening for pulmonary complications (lung fibrosis and pulmonary hypertension) has become standard in the management of SSc. This is now adopted in all European scleroderma centres and incorporated in recommendations for international societies including the European Society of Cardiology (ESC) and European Respiratory Society (ERS) **[f]** and the Expert Panel on Outcomes Measures in PAH related to Systemic Sclerosis (EPOSS) **[g]**. As a result, historically poor outcomes have been positively impacted **[h]**.

In conclusion, our work has impacted on overall outcome in SSc, appropriate follow up and screening of cases and use of broad-spectrum immunosuppression in appropriate cases and has helped to define current standards of care for a disease with high medical burden and the highest case-specific mortality of any rheumatic condition.

5. Sources to corroborate the impact

[a] Patient details can be verified from local audit and through the hospital activity figures. Contact details for clinical audit lead for Rheumatology provided.

[b] http://www.rheumatology.org/Practice/Clinical/Classification/Classification_Criteria_for_Rheumatic_Diseases

[c] This was independently validated by data from a large North American trial, the scleroderma lung study: Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, Arriola E, Silver R, Strange C, Bolster M, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel DE, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006 Jun 22;354(25):2655-66. PubMed PMID: 16790698. http://doi.org/10.1056/NEJMoa055120

[d] Kowal-Bielecka O, Landewe R, Avouac J, et al.; EUSTAR Co-Authors. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis. 2009 May;68(5):620-8. http://dx.doi.org/10.1136/ard.2008.096677
References Hoyles et al. 2006 in the recommendation "In view of the results from two high-quality RCT and despite its known toxicity, cyclophosphamide should be considered for the treatment of SSc-related interstitial lung disease (SSc-ILD)" (see ref. 63)

[e] For example, in Canada: Walker KM, Pope J; Scleroderma Clinical Trials Consortium;

Canadian Scleroderma Research Group. Expert agreement on EULAR/EUSTAR recommendations for the management of systemic sclerosis. J Rheumatol. 2011 Jul;38(7):1326-8. http://dx.doi.org/10.3899/jrheum.101262
This paper reports a survey of members of the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research Group as to their level of agreement with the European guidelines (above). It concludes that "the EULAR/EUSTAR recommendations for the treatment of SSc are relatively well accepted among the world's SSc experts." The survey used a 1-9 ranking, and 85% of respondents put the recommendation on cyclophosphamide in the top three categories.

[f] Galiè N, Hoeper MM, Humbert M, et al.; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009 Oct;30(20):2493-537. http://dx.doi.org/10.1093/eurheartj/ehp297
These guidelines reference three of our papers (ref 1: Simonneau et al 2009; ref 88: Williams et al 2006; ref 114: Mukerjee et al 2003).

[g] Avouac J, Huscher D, Furst DE, Opitz CF, Distler O, Allanore Y; for the EPOSS group. Expert consensus for performing right heart catheterisation for suspected pulmonary arterial hypertension in systemic sclerosis: a Delphi consensus study with cluster analysis. Ann Rheum Dis. 2013 Feb 20 http://dx.doi.org/10.1136/annrheumdis-2012-202567

[h] Following paper showed that in the 1990s: "the lung (both pulmonary hypertension and PF) is the primary cause of scleroderma-related deaths": Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007 Jul;66(7):940-4. http://doi.org/10.1136/ard.2006.066068