Institution: King's College London

Unit of Assessment: 1- Clinical Medicine

Title of case study: Using intensive conventional drug treatment to optimise clinical outcomes in rheumatoid arthritis

1. Summary of the impact

An estimated 1% of UK adults suffer from rheumatoid arthritis and the long-term pain and disability associated with it, Historically, however, treatments focused on relieving symptoms and did not control the arthritis itself or prevent disability. An extensive series of clinical trials and associated research programmes at King's College London (KCL) over 20 years has now significantly improved treatment recommendations and thus quality of life for thousands of rheumatoid arthritis patients in the UK, Europe and other countries. Multicentre trials of intensive treatments using conventional drugs have extended the range of drugs available, established the effectiveness of early intensive treatment, and shown that early combination therapies are safe.

2. Underpinning research

A major chronic condition with high care costs: Rheumatoid arthritis is a long-term condition affecting 1% of UK adults. Historically patients were treated conservatively and many became disabled. In 2000 alone in the UK, this resulted in medical costs of over £1 billion and social care costs of £3.5 billion.

A 20-year initiative against rheumatoid arthritis: Since 1993, Professor Scott and his colleagues at KCL have made important contributions to improving the management of rheumatoid arthritis. During this time they have led 21 randomised controlled trials (17 completed and published, 2 in analysis and 2 in progress; 14 funded by external grants) and published 9 systematic reviews on the treatment of rheumatoid arthritis (all funded by external grants). These trials and systematic reviews have been supported by 38 observational and qualitative studies, and 48 editorials and reviews on rheumatoid arthritis management.

The KCL team's underpinning research has involved extensive collaboration between academic and clinical units in the UK and other European countries. This research has focused on patients with very active forms of the disease in its early stages, on how disease activity can be controlled and on what approaches would ensure that optimal treatment strategies were adopted throughout the UK and beyond.

Early, intensive therapy is optimal: KCL's sustained clinical research programme concluded that the best clinical outcomes are achieved when patients are treated early with combinations of different drugs. Another key finding was that the intensity of therapy is a more important factor than the specific drugs. Treating patients late, with single agents, is less beneficial.

Six publications indicate the wide range of evidence generated. Five of these report on multicentre trials of 90–466 patients lasting 12–36 months; the sixth is a systematic meta-analysis of individual studies that provides confirmatory evidence. These papers provide:

a. Evidence to extend the range of conventional drugs to include leflunomide [1]
b. Confirmatory evidence that early treatment is beneficial and prevents joint damage [2]
c. Evidence that drug combinations early in the disease minimise disability and prevent joint damage [3]
d. An indication of the benefits and risks of adding steroids in established disease [4]
e. An indication of the limitations of delaying intensive treatment until late rheumatoid disease [5]
f. A meta-analysis to confirm the substantial benefits of intensive combination therapy [6].

The research at KCL involved Professor Scott (1993–present), Professor G Panayi (1993–2006, Arthritis Research Campaign Professor), Dr E Choy (1993–2010, Reader) and Dr G Kingsley (1993–present, Reader and later Professor).

3. References to the research

1. **Scott DL**, Smolen JS, Kalden JR, Van De Putte LBA, Larsen A, Kvien TK, Schattenkirchner M, Nash P, Oed C, Loew-Friedrich I: European Leflunomide Study Group.. Treatment of active rheumatoid arthritis with leflunomide: Two-year follow-up of a double-blind, placebo-controlled trial versus sulfasalazine. *Ann Rheum Dis.* 2001;60:913–23.

2. **Choy EH, Scott DL, Kingsley GH,** Williams P, Wojtulewski J, Papasavvas G, Henderson E, Macfarlane D, Erhardt C, Young A, Plant MJ, **Panayi GS**. Treating rheumatoid arthritis early with disease modifying drugs reduces joint damage: a randomised double blind trial of sulphasalazine vs diclofenac sodium. *Clin Exp Rheumatol*. 2002;20:351–8.

3. **Choy EH**, Smith CM, Farewell V, Walker D, Hassell A, Chau L, **Scott DL**: CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) Trial Group**.** Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis.* 2008;67:656–63.

4. **Choy EH, Kingsley GH,** Khoshaba B, Pipitone N, **Scott DL**:Intramuscular Methylprednisolone Study Group**.** A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. *Ann Rheum Dis*. 2005; 64:1288–93.

5. Symmons D, Tricker K, Harrison M, Roberts C, Davis M, Dawes P, Hassell A, Knight S, Mulherin D, **Scott DL**: British Rheumatoid Outcome Study Group. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs – results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. *Rheumatology*. 2006;45:558–65.

6. **Choy EH,** Smith C, Doré CJ, **Scott DL**. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology*. 2005;44:1414–21.

Grants

Over £8 million has been raised in peer-reviewed grants to support the ongoing research programme. This includes ~£2M from MRC, over £1.5M from Arthritis Research UK, more than £4M from NIHR (and NHS R&D), as well as funding from Pharmacia, Hoechst and Aventis.

4. Details of the impact

A new approach to rheumatoid arthritis care: The 2009 National Institute for Health and Clinical Excellence (NICE) guidelines for rheumatoid arthritis [7], draw heavily on research by KCL's Professor Scott and colleagues, referencing 10 of their publications and changing the way that care is delivered for people with rheumatoid arthritis in England.

The guidelines were published by NICE in collaboration with the Royal College of Physicians and the National Collaborating Centre for Chronic Conditions. They include several key priorities for implementation, the most important of which was that "*people with newly diagnosed active rheumatoid arthritis should be offered a combination of disease-modifying anti-rheumatic drugs including methotrexate and at least one other disease modifying drug plus short-term steroids as soon as possible and ideally within 3 months of the onset of persistent symptoms*".

This recommendation depended on the following research evidence:

a. Early treatment with disease-modifying drugs is effective at limiting disability
b. Intensive combination therapy is more effective than treatment with one drug only

c. Conventional drugs, including leflunomide, are the mainstay of treatment.

The evidence favouring intensive treatment was based on a large body of international research, and one specific guidance point was a direct consequence of the KCL group's work – the recommendation to use combinations of disease-modifying drugs. The most crucial KCL research contributions were those showing that using two or more conventional disease-modifying treatments are effective and that these appear highly cost-effective in early rheumatoid arthritis. This approach is also endorsed by the NICE Quality Standard for rheumatoid arthritis, published in June 2013 [8].

Impact on treatment in the UK, Europe and beyond: A number of further measures have been taken to promote the use of intensive treatment in early rheumatoid arthritis in the UK as a result of KCL's work, including the Report from the National Audit Office on Rheumatoid Arthritis (2009) [9] and the National Audit for Early Arthritis led by the Healthcare Quality Improvement Partnership [10]. The NHS Best Practice Tariff for early inflammatory arthritis in 2013/4 Payment by Results also emphasises the importance of early awareness, regular follow-up and appropriate titration (progressive intensification) of therapy [11]. The British Society for Rheumatology guideline also supports this approach [12].

Other national and international guidance, including the Scottish Intercollegiate Network Guidance for the management of early rheumatoid arthritis [13], the European (EULAR) guidance for the management of rheumatoid arthritis [14, 15] and North American guidance [16] have also drawn upon the research of Professor Scott and his colleagues.

Impact on patients: Professor Scott and his colleagues have also published evidence that the management of rheumatoid arthritis is improving as a result of their work. Fewer patients have uncontrolled active disease, joint replacement needs are declining, and inpatient care is falling. However, they have also shown that uptake of intensive treatment approaches remains suboptimal and that greater efforts to translate evidence into practice are still needed [17, 18]. Patients' organisations' advice makes reference to the benefits of early combination treatment [19, 20].

The impact of the research undertaken at KCL has been achieved through the extensive efforts made by the group to disseminate evidence that intensive therapy is effective. These include:

a. Serving on national bodies overseeing clinical practice and standards: Professors Panayi and Scott were both Presidents of The British Society for Rheumatology; Dr Kingsley chaired its External Relations Committee
b. Working with patient groups: Professor Panayi was Chief Medical Adviser to the National Rheumatoid Arthritis Society (NRAS). Professor Scott Chaired the Scientific Section of the Arthritis and Musculoskeletal Alliance (ARMA) and co-ordinated its working group for Standards of Care in Inflammatory Arthritis
c. Contributing to UK and European Guidelines: Professor Scott served on two guidelines groups for rheumatoid arthritis: the National Institute for Health and Clinical Evidence (NICE) group and the European League Against Rheumatism (EULAR) group.

5. Sources to corroborate the impact

Key UK guidance

7. National Institute for Health and Clinical Excellence. Rheumatoid arthritis: NICE guideline. 2009. http://www.nice.org.uk/nicemedia/live/12131/43327/43327.pdf

8. National Institute for Health and Clinical Excellence. Quality standard 33: Rheumatoid arthritis. 2013. http://publications.nice.org.uk/quality-standard-for-rheumatoid-arthritis-qs33

Other UK guidance and reports

9. National Audit Office. Services for people with rheumatoid arthritis. Stationery Office, 2009. http://www.nao.org.uk/wp-content/uploads/2009/07/0809823.pdf

10. National Clinical Audit of Rheumatoid and Early Arthritis. 2013. http://www.hqip.org.uk/new-national-clinical-audits-for-kidney-disease-and-arthritis/

11. Department of Health. Payment by Results Guidance for 2013–14. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf

12. Chakravarty K et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. 2008. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf

13. Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis. Edinburgh: SIGN; 2011. (SIGN publication no. 123).Available from URL: http://www.sign.ac.uk/pdf/sign123.pdf

European guidance

14. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JW, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G, van Vollenhoven R, Winthrop KL, Wong J, Zink A, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 2010;69:964–75.
Also EULAR. EULAR 2013 Rheumatoid Arthritis Management Recommendations, EULAR Data on File, 2013. See http://www.eular.org/myUploadData/files/EULAR%20RA%20recommendations%20FINAL.pdf

15. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewé R, Smolen JS, Aletaha D. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:995–1003.

International guidance

16. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2012;64:625–39.

Editorials and reviews

17. Deighton C, **Scott DL**. Treating inflammatory arthritis early. *BMJ*. 2010;341:c7384.

18. **Scott DL**, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376:1094–108.

Patients' organisation sources

19. National Rheumatoid Arthritis Society: Deighton C. Combination therapy for rheumatoid arthritis 2009/2011. http://www.nras.org.uk/about_rheumatoid_arthritis/newly_diagnosed/which_drugs_are_used/combination_therapy_for_rheumatoid_arthritis.aspx

20. Arthritis and Musculoskeletal Alliance. Standards Of Care For Inflammatory Arthritis. http://arma.uk.net/wp-content/uploads/pdfs/ia06.pdf