Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Improving treatment outcomes for patients with rheumatoid arthritis

1. Summary of the impact

When anti-TNF therapies (which block tumour necrosis factor) were first licensed in 1999 only a few hundred patients with rheumatoid arthritis had received them, most for relatively short periods of time. Although the drugs represented a major breakthrough, 'real-world' effectiveness and safety were unproven. Research at the University of Manchester (UoM) has addressed this knowledge gap and has successfully refined the ways in which anti-TNF drugs are used around the world, leading directly to more effective prescribing and improved patient outcomes. The research has also provided strong evidence that women do not need to discontinue anti-TNF treatment prior to conception.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Rheumatoid arthritis (RA) is a common condition, affecting 1% of adults and causing chronic pain, disability, loss of work and early mortality. Standard treatments (e.g. methotrexate (MTX)) are not effective in all patients and have a range of undesirable side-effects, including nausea and headaches.

UoM launched The British Society for Rheumatology Biologics Register (BSRBR) in 2001 and it is now the world's largest prospective cohort study of anti-TNF treated RA patients. This ongoing study, funded by the British Society for Rheumatology (BSR), has recruited and continues to follow over 16,000 patients starting anti-TNF and related therapies alongside a control group of patients receiving standard therapy. The research focuses on measuring 'real-world' effectiveness in terms of: reducing disease activity (painful and swollen joints) and disability; quantifying the risk of adverse events. The project's first major publication was in 2005.

Key researchers:

- **Deborah Symmons** (Clinical Epidemiologist 1991-2004; Professor of Rheumatology 2004-date)
- **Alan Silman** (Professor of Rheumatology 1992-2011)
- **Kimme Hyrich** (Research Fellow 2001-2005; Clinical Senior Lecturer 2006-2012; Reader 2012-date)
- **Mark Lunt** (Research Fellow 1999-2001 ; Lecturer 2001-2004 ; Senior Lecturer 2004 ; Reader 2004-date)
- **William Dixon** (Clinical Research Fellow 2004-2008; Lecturer 2009-2010; Clinical Senior Lecturer 2010-date)
- **Suzanne Verstappen** (Drug Studies Coordinator 2007-2009; Research Associate 2009; Senior Research Fellow 2010-date)

The key research outputs of this study include the following:

1. We were the first to demonstrate a clear benefit, in terms of greater reduction in disease activity, among patients continuing their background MTX therapy, despite being resistant to MTX when taken without anti-TNF(1).
2. We were the first to quantify the response to a second anti-TNF agent in patients who either failed to respond or experienced an adverse reaction to their first anti-TNF agent (2).
3. We were the first to demonstrate that the benefits of anti-TNF therapy, in terms of improvements in disability, are independent of the severity of the inflammation present at the start of therapy (3).
4. The large size of the study has enabled us to quantify the risk of tuberculosis and establish a differential risk between anti-TNF therapies. We have demonstrated that the risk is

substantially higher with anti-TNF monoclonal antibodies (adalimumab, infliximab) than with recombinant receptor proteins (etanercept) (4).
5. We identified a previously unknown increased risk of bacterial intracellular infections (e.g. salmonella and listeria) (5).
6. We have published the largest collection of robust prospectively collected pregnancy outcome data in women with RA who were inadvertently exposed to biologic treatment at conception. This found no increase in pregnancy complications or congenital abnormalities (6).

3. References to the research

1. **Hyrich KL,** Watson KD, **Silman AJ, Symmons DP**; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford). 2006; 45:1558-65. DOI: 10.1093/rheumatology/kel149

2. **Hyrich KL, Lunt M,** Watson KD**, Symmons DP**, **Silman AJ**; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis & Rheumatism*. 2007;56:13-20. DOI: 10.1002/art.22331

3. **Hyrich KL**, Deighton C, Watson KD; BSRBR Control Centre Consortium, **Symmons DP**, **Lunt M**; British Society for Rheumatology Biologics Register. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. *Rheumatology* (Oxford). 2009;48:1323-7. DOI: 10.1093/rheumatology/kep242

4. **Dixon WG, Hyrich KL,** Watson KD**, Lunt M,** Galloway J, Ustianowski A; BSRBR Control Centre Consortium, Symmons DP; BSR Biologics Register. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Annals of the Rheumatic Diseases*. 2010;69:522-8.DOI: 10.1136/ard.2009.118935

5. **Dixon WG,** Watson K, **Lunt M, Hyrich KL**, **Silman AJ, Symmons DP**; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis & Rheumatism*. 2006;54(8):2368-76. DOI: 10.1002/art.21978

6. **Verstappen, S,** King, Y, Watson, K**, Symmons, D, Hyrich, K**. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Annals of the Rheumatic Diseases*. 2011;70(5): 823-826. DOI: 10.1136/ard.2010.140822

4. Details of the impact

See section 5 for corroborating sources S1-S9.

Research outputs from the BSRBR study have refined the way anti-TNF therapies are prescribed in RA with a goal of maximising patient benefit and minimising patient risk.

Pathways to impact have included:
1. Membership of UoM key researchers on national and international rheumatoid arthritis guideline working parties;
2. Submission of data to National Institute for Health and Clinical Excellence (NICE) to support technology appraisal;
3. Collaboration with national arthritis charities including Arthritis Research UK and the National Rheumatoid Arthritis Society.

Reach and significance of the impact

1. NICE guidance is the most important factor in determining which new therapies can be prescribed to patients in the UK. If guidance does not exist for a new technology or if guidance

does not allow a technology, funding is likely to be denied. This study has contributed to one recent NICE technology appraisal (TA) and several previous appraisals now superseded.

(a) Impact: Improved treatment outcomes for patients
By demonstrating the benefits of combining anti-TNF treatments with continued background MTX (unless contra-indicated) the study has contributed directly to NICE TA195 (published 2010 and still in effect in 2013). The previous guidelines did not specify that MTX treatment should be continued (TA36). However, we demonstrated that, year on year from 2001-8, the proportion of patients continuing MTX with anti-TNF increased in the UK, with subsequent improvements in treatment responses (S1,S2).

(b) Impact: Improved access to controlled treatments for UK patients
By demonstrating the benefits of switching between anti-TNF agents when a first has been ineffective, the study contributed to NICE TA195. This new guidance allows sequential anti-TNF use if rituximab is contraindicated – an approach that was not previously allowed under NICE guidance (TA36) (S1).

2. Output from the BSRBR has also contributed to new national guidelines outlining eligibility criteria for anti-TNF. The study indicated that the drugs should no longer be reserved for patients with high disease activity, but should instead be used in all patients with ongoing disease activity resistant to standard treatments (S3). This has improved choice and access for patients within this subgroup.

3. Our research into the risk of intracellular infections such as listeria and salmonella has led to new information being incorporated into Arthritis Research UK Drug Information Leaflets (provided to every patient in the UK considering anti-TNF therapies). It has also prompted the FDA to update product labelling. Specifically, the new information warns of the risk of consuming undercooked or unpasteurised foods, similar to the advice provided to pregnant women. Our research has shown that updating the Arthritis Research UK Drug Information Leaflets in 2006 led to a 73% decrease in new cases of intracellular infection in RA patients exposed to anti-TNF in the UK from 2007-12 (S4, S5). This leaflet remains in print today.

4. Our publications on outcomes among women exposed to anti-TNF therapy during pregnancy have contributed to a significant change in product labelling. It is now indicated that women can continue anti-TNF therapies into pregnancy if clearly needed, as opposed to previous labelling that treatment should be discontinued in the months leading up to conception (which often resulted in a disease flare). This is a major change within rheumatology, as other non-biologic DMARDs are contra-indicated in pregnancy, many with the risk of teratogenicity. Our research offers a safer option for disease control in the months leading up to conception.

5. Our research data are contributing to the training of new doctors, as well as to the maintenance of certification among established physicians, with data featuring in ‘Up-to-Date’, an evidence-based online guide for physicians on current best practice. In particular, we are the only group to have published a differential risk of tuberculosis across anti-TNF therapies, which may direct choice of treatment in high-risk cases (S6).

6. Finally, the BSRBR is proving to be an invaluable resource for patients and physicians across the UK and internationally, for pharmaceutical companies who manufacture the drugs and for international drug regulators (e.g. MHRA, FDA, EMA) (S7-S9). With data on over 20,000 patients and >80000 adverse events, it has become a vital and accessible resource for up-to-date and unpublished safety information. Physicians can access information directly from the investigators, and pharmaceutical companies and regulators are provided with detailed serious adverse event information and publications to ensure effective risk management of these new therapies.

The Director of Vigilance and Risk Management of Medicines at the MHRA states: ‘The greatest regulatory impact of the BSRBR has been in helping to define the clinical safety profile of biological agents in the treatment of rheumatoid arthritis, particularly over the long term. The unique scale of

the register provides the opportunity to study the risks of rare serious safety concerns with unusual precision.' (S7)

The Chief Executive of the National Rheumatoid Arthritis Society underlines the significance of the BSRBR research for those living with RA: 'This information has supported our campaign for widening access to anti-TNF therapies, especially in patients who do not respond to their first biologic. The study has also been an invaluable source of information about the safety of these treatments.' (S9)

The manufacturers of newer agents continue to approach UoM for information on how to join this important study, thereby ensuring the long-term observation of patients starting new therapies for arthritis.

5. Sources to corroborate the impact

S1. National Institute for Health and Care Excellence. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. TA195. London: National Institute for Health and Care Excellence, 2010. Available from: www.nice.org.uk/guidance/TA195
NICE TA 195 specifies a treatment algorithm in patients who fail a first anti-TNF therapy, including choice in patients intolerant of MTX, with data or analyses from the BSRBR referenced on pp 18-49.

S2. **Hyrich KL, Watson KD, Lunt M, Symmons DP**; British Society for Rheumatology Biologics Register (BSRBR). Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. *Rheumatology* (Oxford). 2011; 50:117-23. DOI: 10.1093/rheumatology/keq209

S3. BSR/BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biologic therapy (http://www.rheumatology.org.uk/includes/documents/cm_docs/2010/r/2_ra_guidelines_on_eligibility_criteria_for_the_first_biological_therapy.pdf ; DOI: 10.1093/rheumatology/keq006b) state that biologic therapies should be offered to RA patients with a DAS28 >3.2 and at least three tender and three swollen joints.

S4. Arthritis Research UK Drug Information Leaflets e.g. http://www.arthritisresearchuk.org/arthritis-information/drugs/etanercept.aspx
and http://www.fda.gov/Drugs/DrugSafety/ucm270849.htm warn patients on anti-TNF therapy that they should avoid foods such as unpasteurised cheeses and undercooked meats.

S5. **Davies R, Dixon WG, Watson KD, Lunt M**; BSRBR Control Centre Consortium, **Symmons DP, Hyrich KL**; BSRBR. Influence of anti-TNF patient warning regarding avoidance of high risk foods on rates of listeria and salmonella infections in the UK. *Annals of the Rheumatic Diseases*. 2013 ;72:461-2. DOI: 10.1136/annrheumdis-2012-202228

S6. www.uptodate.com cites data from the BSRBR as the only source of information on the differential risk of TB across anti-TNF agents. See uptodate.com topics 'Tumor necrosis factor-alpha inhibitors: Risk of bacterial, viral, and fungal infections' (updated 2013) and 'Tumor necrosis factor-alpha inhibitors and mycobacterial infections' (updated 2013).

S7. Letter from Director of Vigilance and Risk Management of Medicines, MHRA.

S8. Survey of BSR Membership, 2012.

S9. Letter from Chief Executive, National Rheumatoid Arthritis Society.