Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: B cell depletion: an effective therapy in rheumatoid arthritis

1. Summary of the impact

Research at UCL pioneered B cell depletion to treat rheumatoid arthritis (RA) and also stimulated the development of B-cell-directed therapies for other autoimmune rheumatic, haematological and neurological diseases. Now NICE approved, B cell depletion (based on rituximab) in RA is as effective as the alternative (anti-TNFα drugs) and an option for patients unable to gain benefit from anti-TNFα drugs. Rituximab offers drug-cost savings of up to £5,000/annum/patient and for many is a more convenient therapy, being given as an infusion only every five months apart, or more. B cell depletion has also proved to have an excellent safety profile, with many receiving repeated courses of treatment. As a consequence of UCL research, rituximab has brought substantial benefit to patients with many autoimmune diseases, including over 200,000 who have been treated with rituximab for RA so far.

2. Underpinning research

In the 1980s and early 1990s it was a general view that rheumatoid arthritis (RA) was caused by T cells that attacked specific targets in joints. The consequent release of toxic cytokines by joint macrophages was generally agreed to be responsible for inflammation. Yet, despite more than 20 years of research, no consistently autoreactive T cell had been identified. Research at UCL conducted by Jonathan Edwards and Geraldine Cambridge led to the hypothesis that B cells played an essential role in the pathogenesis of RA **[1]**.

Following anatomical and immunohistochemical studies of normal and diseased human synovium they found that a receptor (CD16) was constitutively expressed on macrophages in synovial lining and to a lesser extent in other sites affected in the disease. The consequence of CD16 activation was to stimulate macrophages to generate TNFα, a powerful pro-inflammatory cytokine known to be involved in joint inflammation. CD16 appeared to be activated by soluble complexes of particular autoantibodies, previously described in RA patients. They suggested that the constant supply of autoantibodies capable of forming these small 'activating' complexes was due to expansion of B cells (responsible for autoantibody generation) in a manner that avoided usual pathways to control their number **[2]**. This led to the hypothesis that removing B cells would reduce the inflammatory stimulus and also break the vicious cycle of autoreactive B cell expansion.

Towards the end of the 1990s, Roche developed a drug, rituximab (which binds the CD20 marker on all mature B cells), for the treatment of B-cell cancers notably lymphomas. Edwards and Cambridge were quick to recognise that since both B-cell lymphoma and RA involved uncontrolled proliferation of B cell clones, rituximab might well be what they had been waiting for to treat patients with RA. Proof of concept followed with the clinical success of a small trial of the B-cell-depleting agent, rituximab, in 5 patients with intractable RA in 1998/9 by the UCL team, and confirmed by them in a larger cohort **[3, 4]**.

The first randomised trial started in 2002 and was published in NEJM in 2004 **[5]**. The results indicated that rituximab produced results in patients with RA that at least matched those of patients treated with TNFα blockade. Successful treatment of patients with systemic lupus erythematosus by the group followed **[6]**. Rituximab was licensed for the treatment of patients with RA in 2006.

3. References to the research

[1] Edwards JCW, Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol. 2006 6(5):394-403. http://dx.doi.org/10.1038/nri1838

[2] Edwards JC, Cambridge G, Abrahams VM. Do self-perpetuating B lymphocytes drive human autoimmune disease? Immunology. 1999 Jun;97(2):188-96. http://dx.doi.org/10.1046/j.1365-2567.1999.00772.x

[3] Edwards JC, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. Rheumatology (Oxford). 2001 Feb;40(2):205-11. http://dx.doi.org/10.1093/rheumatology/40.2.205

[4] Leandro MJ, Edwards JC, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. Ann Rheum Dis. 2002 Oct;61(10):883-8. http://dx.doi.org/10.1136/ard.61.10.883

[5] Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81. http://dx.doi.org/10.1056/NEJMoa032534

[6] Leandro MJ, Edwards JCW, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum. 2002 Oct;46(10):2673-7. http://dx.doi.org/10.1002/art.10541

4. Details of the impact

As a result of the research described above, rituximab is now in widespread use as a treatment for RA, with usage rising every year **[a]**. By the end of July 2013, Roche estimated that 228,801 patients have been treated with rituximab for RA **[b]**.

In March 2006, the FDA approved rituximab for use in combination with methotrexate in adult patients with moderately to severely active RA who have had an inadequate response to anti-TNFα therapy. Approval by the European Medicines Agency (EMA) came in July of the same year. Towards the end of 2006, a consensus statement and guidance document on the use of rituximab for routine care of patients with RA was issued by the European League Against Rheumatism (EULAR), describing the treatment as "a major advance in the therapeutic armamentarium for patients with rheumatoid arthritis" **[c]**.

In 2007, NICE issued guidance (updated in 2011) recommending rituximab as follows:

> *Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor* **[d]**.

British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) issued further guidelines on the use of rituximab in 2010 **[e]**. Rituximab was also recommended in guidelines issued by the American College of Rheumatology (ACR) in 2008, updated in 2012 **[f]**.

Benefits to patients

The use of rituximab extends treatment to those patients who cannot have anti-TNFα drugs because of contra-indications (a history of cancer or pre-malignant conditions and patients with history of recurrent and/or serious infections or considered to be at a high risk of infection). Data from a collaboration of different European registries shows that 36% of patients received rituximab as first-line biologic **[g]**.

Rituximab is also indicated as a second line treatment for patients where anti-TNFα drugs failed, and this amounts to between 30 and 40% of patients that are considered for biologic therapy. One patient, for whom three anti-TNFα drugs had failed, described the impact of rituximab as follows:

"*Blood tests showed that my levels of inflammation were the lowest that they'd been for years. I was less tired and had more mental and physical energy. I resumed several of my hobbies… Mabthera transformed my life… the effects have been radical. I can truthfully say that I haven't experienced this level of wellbeing for many years*" **[h]**.

A major advantage of rituximab is that it can be given as two infusions two weeks apart (or four smaller weekly injections), with effects persisting for 6-12 months thereafter. From the patient's perspective, this is a more convenient schedule of administration than other biologics (typically administered 12-24 times per year). Furthermore, as the UCL team and others have demonstrated, rituximab infusions can be repeated on an annual basis for several years. Loss of response to rituximab in patients with RA that have previously responded well is rare, and it is well tolerated with excellent safety profiles in RA and in patients with many other conditions **[i]**.

Economic impacts

Rituximab costs £5,000 per annum less than other biologics. In the UK it is generally the next choice before other more expensive alternatives such as tocilizumab, abatacept or belimumab. Use in patients in this setting has already generated considerable savings to the NHS. The economic impact of rituximab has been greater in low and middle income countries (for example, Brazil) where the lower cost of rituximab makes it the first-line biologic for RA **[j]**.

Use of rituximab in other conditions

The success of B cell depletion therapy in RA has led directly to it being used for autoimmune rheumatic diseases (such as systemic lupus erythematosus, ANCA associated vasculitis, Behcets syndrome, myositis, anti-phospholipid syndrome, Sjogren's syndrome, neuromyelitis optica). Rituximab is licensed for ANCA-associated vasculitis **[k]**, is approved for funding by NHS England for SLE **[l]**, and has been nationally commissioned for the treatment of Behcets disease **[m]** and neuromyelitis optica **[n]**.

5. Sources to corroborate the impact

[a] As reported by Roche (the drug's manufacturers) in their 2013 Half Year Report. http://www.roche.com/hy13e.pdf See p.22.

[b] Email correspondence from Roche. Available on request.

[c] Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge N, Burmester GR, Dougados M, Ferraccioli G, Jaeger U, Klareskog L, Kvien TK, Martin-Mola E, Pavelka K; Working Group on the Rituximab Consensus Statement. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Feb;66(2):143-50. Epub 2006 Oct 26. http://dx.doi.org/10.1136/ard.2006.061002

[d] NICE technology appraisal guidance 195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. http://publications.nice.org.uk/adalimumab-etanercept-infliximab-rituximab-and-abatacept-for-the-treatment-of-rheumatoid-ta195/evidence-and-interpretation

[e] Bukhari M, Abernethy R, Deighton C, Ding T, Hyrich K, Lunt M, Luqmani R, Kiely P, Bosworth A, Ledingham J, Ostör A, Gadsby K, McKenna F, Finney D, Dixey J; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. Rheumatology (Oxford). 2011 Dec;50(12):2311-3. http://dx.doi.org/10.1093/rheumatology/ker106a

[f] 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 (Hoboken). 2012 May;64(5):625-39. http://dx.doi.org/10.1002/acr.21641

[g] Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, Gabay C, van Riel PL, Nordström DC, Gomez-Reino J, Pavelka K, Tomsic M, Kvien TK, van Vollenhoven RF. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. Ann Rheum Dis. 2011 Sep;70(9):1575-80. http://dx.doi.org/10.1136/ard.2010.148759

[h] Jean Bailey-Dering. My experience of rituximab (Mabthera) infusions. 03/12/08. Case study on website of the National Rheumatoid Arthritis Society. http://www.nras.org.uk/about_rheumatoid_arthritis/living_with_rheumatoid_arthritis/case_studies/female/my_experience_of_rituximab_mabthera_infusions.aspx

[i] Tony HP, Burmester G, Schulze-Koops H, Grunke M, Henes J, Kötter I, Haas J, Unger L, Lovric S, Haubitz M, Fischer-Betz R, Chehab G, Rubbert-Roth A, Specker C, Weinerth J, Holle J, Müller-Ladner U, König R, Fiehn C, Burgwinkel P, Budde K, Sörensen H, Meurer M, Aringer M, Kieseier B, Erfurt-Berge C, Sticherling M, Veelken R, Ziemann U, Strutz F, von Wussow P, Meier FM, Hunzelmann N, Schmidt E, Bergner R, Schwarting A, Eming R, Hertl M, Stadler R, Schwarz-Eywill M, Wassenberg S, Fleck M, Metzler C, Zettl U, Westphal J, Heitmann S, Herzog AL, Wiendl H, Jakob W, Schmidt E, Freivogel K, Dörner T; GRAID investigators. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis Res Ther. 2011 May 13;13(3):R75. http://dx.doi.org/10.1186/ar3337.

[j] Data on prescribing costs in Brazil. Copy of files available on request.

[k] SPC for rituximab; http://www.medicines.org.uk/emc/medicine/2570#POSOLOGY

[l] Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. September 2013. Reference: NHS ENGLAND A13/PS/a2. Copy available on request.

[m] National Specialised Commissioning Team. Behçet's Syndrome Service Specification. April 2012. Copy available on request.

[n] National Specialist Commissioning Team. Neuromyelitis Optica Service Specification. 2012-3. Copy available on request.