

Impact case study (REF3b)

Institution: Imperial College London
Unit of Assessment: 01 Clinical Medicine
Title of case study: Threefold Increase in the Use of Anti-TNF in the Treatment of Common Chronic Inflammatory Conditions
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Rheumatoid arthritis (RA) is a costly and debilitating autoimmune disorder that is characterized by joint pain, stiffness, and impaired functionality. Work at Imperial College identified tumour necrosis factor (TNF) as a key therapeutic target in the abnormal joint lining in RA. This discovery revolutionised the treatment of Rheumatoid Arthritis and other inflammatory conditions. Since 2008 the anti-TNF inhibitor infliximab (Remicade®) has been used to treat more than 1.3 million patients worldwide who have inflammatory conditions such as plaque psoriasis, rheumatoid arthritis, psoriatic arthritis, adult and paediatric Crohn's disease, ulcerative colitis, and ankylosing spondylitis. The work has had ongoing impact across the globe for the treatment of inflammatory diseases. It established the concept of biological therapy demonstrating the use of an antibody to block a cytokine and treat chronic inflammatory disease. In 2012 Remicade® was the 4th best-selling worldwide drug with total global sales of \$7.67 Billion.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Key Imperial College London researchers: Professor Sir Marc Feldmann, Professor of Cellular Immunology (1992-2011) now at Oxford. Dr Richard Williams, Reader (1989-2011) now at Oxford. Professor Fionula Brennan, Professor of Cytokine Immunopathology (1986-2011) Professor Sir Ravinder Maini, Professor of Rheumatology (1979-2011) Professor Peter Taylor, Professor of Clinical Research (1990-2011) now at Oxford.</p> <p>RA is a costly and debilitating autoimmune disorder that is characterized by joint pain, stiffness, and impaired functionality. Symptoms arise from the inflammation and degradation of the synovial membrane, causing progressive disability in joint function. As the disease progresses, patients require more frequent invasive procedures (e.g., joint injections, synovectomy) as well as the eventual replacement of affected joints. Consequently, the economic costs of RA are considerable, as the estimated direct and indirect costs of related care in the UK is £8 billion and in the US totals \$19 billion annually.</p> <p>The identification of TNF as a key therapeutic target in the abnormal joint lining in RA, began with observations by Professor Brennan working under the direction of Professor Feldmann at Imperial. The first clinical study, performed at Charing Cross Hospital, published in 1993, enrolled 20 patients with disease refractory to all existing treatment who were given a single infusion of infliximab, a monoclonal antibody to TNF (1). Results in the RA study were dramatic and led to a randomised placebo-controlled trial in collaboration with three other European centres. Remarkably the response rate with the highest dose of infliximab was 79% at 4 weeks in comparison to 8% with placebo. The success of repeated treatments was first demonstrated in a small study (2); however the degree of response was less, partly due to the monoclonal antibody inducing an immune response to itself which limited its effectiveness.</p> <p>Further studies of the mouse model undertaken by Dr Williams at Imperial, under the direction of Professor Feldmann, indicated that combining an anti-TNF monoclonal antibody with a therapy targeting the T cells of the immune system might improve response through synergy and a reduction in immunogenicity. This finding led to combining methotrexate (MTX), already established in the treatment of RA, with infliximab in the next randomised-controlled trial (3, 4).</p> <p>The demonstration of synergy with this combination of therapy, in the absence of increased toxicity, has set the gold standard of pharmacological management. Further clinical studies led by Professors Maini and Feldmann demonstrated that biologic TNF inhibition plus methotrexate markedly inhibits the structural joint damage previously thought to be an irreversible feature of RA (4). Clinical science studies undertaken by Professor Taylor (also at Imperial), working with</p>

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Professors Maini and Feldmann, used biologic TNF inhibitors to investigate the pathobiology of TNF in RA and demonstrated that this cytokine regulates inflammatory cell migration to joints via modulation of chemokines and adhesion molecules as well as joint vascularity (5).

Infliximab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. Infliximab won its initial approval by the FDA for the treatment of Crohn's disease in August 1998.

3. References to the research (indicative maximum of six references)

(1) Elliott, M.J., Maini, R.N., Feldmann, M., Long-Fox, A., Charles, P., Katsikis, P., Brennan, F.M., Walker, J., Bijl, H., Ghayeb, J., et al. (1993). Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum*, 36, 1681-1690. [DOI](#). Times cited: 790 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 7.47

(2) Elliott, M.J., Maini, R.N., Feldmann, M., Long-Fox, A., Charles, P., Bijl, H., Woody, J.N. (1994). Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. *Lancet*, 344, 1125-1127. [DOI](#). Times cited: 524 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(3) Maini, R.N., Breedveld, F.C., Kalden, J.R., Smolen, J.S., Davis, D., Macfarlane, J.D., Antoni, C., Leeb, B., Elliott, M.J., Woody, J.N., Schaible, T.F., Feldmann, M. (1998). Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum*, 41, 1552-1563. [DOI](#). Times cited: 967 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 7.47

(4) Lipsky, P.E., van der Heijde, D.M., St Clair, E.W., Furst, D.E., Breedveld, F.C., Kalden, J.R., Smolen, J.S., Weisman, M., Emery, P., Feldmann, M., Harriman, G.R., Maini, R.N.; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. (2000). Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med*, 343 (22), 1594-1602. [DOI](#). Times cited: 1861 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 51.65

(5) Taylor, P.C., Steuer, A., Gruber, J., Cosgrove, D.O., Blomley, M.J.K., Marsters, P.A., Wagner, C.L., McClinton, C., Maini, R.N. (2006). Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in erosive early rheumatoid arthritis. *Arthritis Rheum*, 54, 47-53. [DOI](#). Times cited: 46 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 7.47

The Dr. Paul Janssen Award For Biomedical Research A Symbol of Innovation and Achievement winners in 2008 Marc Feldmann & Ravinder Maini <http://www.pauljanssenaward.com/winners.html>

Key funding:

- Arthritis Research Campaign (2007-2012; £22,500,000), Principal Investigator (PI) M. Feldmann, Institute's major source of research support
- European Union (2008-2013; £833,000) PI M. Feldmann, Mechanisms to attack steering effectors of rheumatoid syndromes with innovated therapy choices.
- Kennedy Institute of Rheumatology Trust funding totalling £3.284M. A breakdown of funding available on request.
- Wyeth Pharmaceuticals (2003-2007; £593,682) PI M. Feldmann, F. Brennan, B. Foxwell, A path to drug discovery.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare; commercial; public policy and services

Main beneficiaries include: patients, industry, NICE, NHS, American College of Rheumatology, Royal College of Nursing

The global continuing impact of this work has been to revolutionise the treatment of Rheumatoid Arthritis and other inflammatory conditions.

Full validation of TNF as a target came about in the form of clinical trials in man, which unequivocally showed significant benefit in most patients treated. Biologic inhibition of TNF, in combination with concomitant methotrexate (MTX), not only improved symptoms and signs of Rheumatoid Arthritis (RA) in many patients, but most dramatically halted the structural damage previously thought to be an inexorably progressive feature of RA. Preservation of functional capability is a consequence of both reduction in disease activity and prevention of joint damage and as such, not surprisingly, the most impressive benefit of biologic TNF inhibitors has been demonstrated when therapy is initiated in the early stages of RA. Biologic anti-TNF therapies have set the height of the bar to which all biologics directed at alternative molecular targets have had to aspire to achieve the magnitude of improvement in symptoms and signs, prevention of joint destruction and preservation or improvement in function.

TNF blockade has changed the rheumatology practice. The introduction of infliximab (among other biological therapies) has changed the way inflammatory bowel diseases and rheumatoid conditions are treated. More importantly, infliximab has offered significant improvement of the quality of life of many patients. In addition, infliximab has changed the natural course of these inflammatory diseases [1].

Infliximab (Remicade®) provides anti-rheumatic activity by inhibiting tumor necrosis factor (TNF). The use of such agents in combination with methotrexate has been shown to be clinically superior to methotrexate alone in controlled clinical trials.

The work has had ongoing impact across the globe for the treatment of inflammatory diseases. In 2012 Remicade was the 4th best-selling worldwide drug with total global sales of \$7.67 Billion [2].

Since 2008 Remicade® has been used to treat more than 1.3 million patients worldwide who have inflammatory conditions such as plaque psoriasis, rheumatoid arthritis, psoriatic arthritis, adult and paediatric Crohn's disease, ulcerative colitis, and ankylosing spondylitis [3].

The National Institute for Health and Clinical Excellence (NICE) currently recommends the use of anti TNF for RA under the following clinical circumstances (clinical guidance 79 Feb 2009): From the recommendations: 2.2.1.1 The tumour necrosis factor alpha (TNF- α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics.

1. Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
2. Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

In 2010 NICE has widened the proposed criteria for treating psoriatic arthritis with Schering-Plough's Remicade® on the National Health Service, improving access to therapies for the disease [4, 5]. "In its updated guidance, NICE advises healthcare professionals to prescribe infliximab (Remicade), etanercept (Enbrel) or adalimumab (Humira) if:

1. The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and
2. The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs), administered either individually or in combination"

Numerous global treatment guidelines, practitioner guides and standards of care have been written to reflect the impact of this discovery [6, 7, 8, 9].

The introduction of anti-TNF created a wider therapeutic field and introduces concept of utilising an antibody to block a cytokine. This concept of biological therapy has led to the development of further new classes of drugs for example [10];

- Anakinra is an interleukin-1 (IL-1) receptor antagonist. Anakinra blocks the biologic activity of naturally occurring IL-1, including inflammation and cartilage degradation associated with rheumatoid arthritis.
- Tocilizumab] (INN, or atilizumab, developed by Hoffmann–La Roche and Chugai and sold under the trade names Actemra and RoActemra) is an immunosuppressive drug, mainly for the treatment of RA. It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) blocking the actions of Interleukin 6 a cytokine that plays an important role in immune response and is used in the treatment of autoimmune diseases, multiple myeloma and prostate cancer.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Cornillie, F. (2009). Ten years of infliximab (Remicade®) in clinical practice: The story from bench to bedside. *European Journal of Pharmacology*, 623, S1-4. [DOI](#).

[2] Global sales figures 2012

<http://www.fiercepharma.com/special-reports/remicade> ([archived](#) on 8th November 2013)

[3] Number of patients treated globally

<http://www.remicade.com/rheumatoid-arthritis/about-remicade> ([archived](#) on 8th November 2013)

[4] NICE widens access to Remicade.

<http://www.nice.org.uk/newsroom/pressreleases/PsoriaticArthritisDrugTreatments.jsp> ([archived](#) on 8th November 2013)

[5] Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and Gastroenterology Commissioning guide Implementing NICE guidance

<http://www.nice.org.uk/media/F95/42/UpdateTA247AndPsoriasisCG.pdf> ([archived](#) on 8th November 2013)

[6] US Guidelines from the American College of Rheumatology (2008 and updated in 2012)

[Recommendations for the use of Disease-Modifying Anti-Rheumatic Drugs and Biologics in the treatment of Rheumatoid Arthritis](#)

[7] National Institute for Health and Clinical Excellence (2010) [Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor](#).

NICE technology appraisal guidance 195. [Archived](#) on 8th November 2013.

[8] Royal College of Nursing (2009) Assessing, managing and monitoring biologic therapies or inflammatory arthritis: Guidance for rheumatology practitioners.

http://www.rcn.org.uk/_data/assets/pdf_file/0004/78565/001984.pdf ([archived](#) on 8th November 2013)

[9] [NICE Guidelines 2009](#) (clinical guidance 79) February 2009 ([archived](#) on 8th November 2013)

[10] [The use of Anakinra](#) ([archived](#) on 8th November 2013)

[The use of Tocilizumba](#) ([archived](#) on 8th November 2013)