Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

REVOLUTIONISING THE TREATMENT OF RHEUMATOID ARTHRITIS

Summary of the impact:

Rheumatoid arthritis is a debilitating inflammatory condition, affecting around 500,000 people in the UK and around 0.5-1% of the adult population worldwide. Using novel techniques to study human synovium, Professor Sir Marc Feldmann and Professor Sir Ravinder Maini from the Kennedy Institute of Rheumatology identified a therapeutic target, TNFα, for treatment of rheumatoid arthritis. Following successful clinical trials, showing the safety and effectiveness of this new target, anti-TNFα antibodies have now become the gold standard treatment for severe rheumatoid arthritis worldwide. In addition to dramatically impacting patient care, anti-TNFα antibodies represent the largest group of therapies against rheumatoid arthritis on the market, with annual sales currently exceeding US$24.4 billion.

Underpinning research:

Since the late 1980s disease-modifying antirheumatic drugs (a term used to describe several medications, which reduce the rate of damage to bone and cartilage) have been widely used to decrease disease activity and prevent joint damage in patients with rheumatoid arthritis. However, many of these drugs have been known to cause serious side effects, such as low white blood cell counts and liver damage. After testing his hypothesis that antigen presentation and cytokines were important in autoimmunity[1] Professor Sir Marc Feldmann first identified tumour necrosis factor alpha (TNFα) as a key therapeutic target for rheumatoid arthritis in 1983[2]. In 1992, Professor Feldmann, his colleague Professor Maini, and their team embarked on a number of significant studies and clinical trials, using monoclonal antibodies against TNFα. These trials showed that inhibition of TNFα was safe and rapidly effective, and led to the development and commercialisation of anti-TNFα as a treatment for rheumatoid arthritis, first approved in 1998 in the US.

The first clinical study, performed at Charing Cross Hospital in 1993, enrolled 20 patients who had previously shown resistance to all existing treatments. After giving them an infusion of cA2, a monoclonal antibody to TNFα, now termed “Infliximab”, patients experienced a dramatic improvement in their symptoms and signs. These results led to a randomised placebo-controlled trial in collaboration with three other European centres. 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 then demonstrated in a smaller study, however, the duration of response diminished, partly due to an immune response against the TNFα antibody itself. Further studies using a mouse model of rheumatoid arthritis indicated that the combination of an anti-TNF monoclonal antibody with therapy targeting T cells might improve the effectiveness. This finding led to the combined use of methotrexate (already established in the treatment of rheumatoid arthritis) with infliximab, in the next randomised controlled trial[3]. The demonstration of synergy with this combination therapy, without increased toxicity, set the gold standard for pharmacological management of rheumatoid arthritis. Additional clinical studies led by the Kennedy Institute showed that biologic TNFα inhibition plus methotrexate markedly inhibits the structural joint damage previously thought to be an irreversible feature of rheumatoid arthritis[4]. In addition, follow-up studies demonstrated that TNFα regulates inflammatory cell migration to joints via modulation of chemokines, adhesion molecules, and joint vascularity[5,6].

The primary research underpinning the impact of anti-TNFα took place at the Kennedy Research Institute between 1993 and 1998. While the Institute was then based at Imperial College London

between 2000 and 2011, the Kennedy Research Institute remained a separate, freestanding division and in August 2011 the Kennedy Institute was fully incorporated into the University of Oxford. Professor Sir Marc Feldmann continues to lead research into the role of cytokines in disease.

References to the research:

1. Bottazzo G.F., Hanafusa T., Pujol-Borrell R., Feldmann M. Role of aberrant HLA-DR expression and antigen presentation in the induction of endocrine autoimmunity. *Lancet* **322** (8359):1115-9 (1983). http://dx.doi.org/10.1016/S0140-6736(83)90629-3 ***First conception of hypothesis that antigen presentation and its regulation by cytokines could be important in the pathogenesis of autoimmunity.***

2. Brennan F.M., Chantry D., Jackson A., Maini R.N., Feldmann M. Inhibitory effect of TNFα antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* **334**(8657):244-247 (1989). http://dx.doi.org/10.1016/S0140-6736(89)90430-3, ***First demonstration that TNFα was a therapeutic target, as blocking TNF also blocked other proinflammatory cytokines, IL-1 in this case.***

3. Maini R.N. et al.Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor a monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* **41**:1552-63 (1998). doi:10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W. ***Paper reporting follow-up randomised controlled trial, which combined the use of methotrexate with infliximab.***

4. Maini R. et al. Infliximab (chimeric anti-tumour necrosis factor a monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* **354**(9194):1932-39 (1999). doi:10.1016/S0140-6736(99)05246-0. ***Reporting findings from additional clinical studies, showing biologic TNFα inhibition plus methotrexate inhibits structural joint damage.***

5. Taylor P.C. et alReduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor alpha blockade in patients with rheumatoid arthritis. *Arthritis Rheum* **43**:38-47 (2000). doi:10.1002/1529-0131(200001)43:1<38::AID-ANR6>3.0.CO;2-L. ***Paper reporting that TNFα regulates inflammatory cell migration to joints via modulation of chemokines, adhesion molecules, and joint vascularity.***

6. Taylor P.C. et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum* **50**:1107-16 (2004). doi:10.1002/art.20123. ***Paper reporting a follow-up study, which demonstrated that TNFα regulates inflammatory cell migration to joints via modulation of chemokines, adhesion molecules, and joint vascularity.***

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Details of the impact:

Rheumatoid arthritis is a persistent inflammatory arthritis of synovial joints that currently affects around 500,000 people in England and an estimated 0.5-1% of the adult population worldwide. Rheumatoid arthritis can lead to pain, deformity and loss of function, work disability, economic losses and premature death. Prior to the development of anti-TNFα therapies, a considerable proportion of patients treated with the available disease-modifying antirheumatic drugs (DMARDs)

were still plagued by premature death rates, and had evidence of persistent disease activity, with many patients remaining wheelchair bound due to ongoing joint damage and disability.

The commercial introduction of anti-TNFα agents from 1999 has profoundly changed the management of severe rheumatoid arthritis throughout the developed world, with over 2 million patients having received this treatment. Anti-TNFα therapy has had a profound impact on the quality of life of patients with rheumatoid arthritis. It is capable of not only controlling symptoms such as pain and stiffness, it can also protect joints from the structural damage which leads to disability. This has also prompted the successful use of anti-TNFα therapy in a number of other immune-inflammatory diseases, such as juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and psoriasis. One study on the effects of anti-TNFα therapy in patients with Crohn's disease showed that it significantly improved the quality of life of patients, by increasing their ability to work and participate in leisure activities, decreasing fatigue, depression, and anger[7]. In addition, whilst TNF inhibition in established disease does not result in cure, evidence is emerging that commencing treatment during early disease can result in drug-free remission[8]. The British Society of Rheumatology issued guidelines on the use of anti-TNFα inhibitors in rheumatoid arthritis in 2001, and the National Institute for Health and Clinical Excellence endorsed the therapy in 2002[9]. The combination of an anti-TNFα agent with methotrexate remains unsurpassed in reducing the signs and symptoms of rheumatoid arthritis and in improving joint destruction[10]. Current UK guidelines also address the optimal use of biologics and disease modifying antirheumatic drugs (including methotrexate) for the management of rheumatoid arthritis[11, 12]. The 2010 European League Against Rheumatism guidelines for the management of rheumatoid arthritis recognise the importance of early introduction of biologic TNFα inhibitors in patients failing to reach a treatment target of remission or low disease activity on conventional, non-biologic synthetic DMARDs[13]. Anti-TNFα therapy is the recommended first line treatment, and if therapeutic response is not achieved within 3-6 months, the guidelines recommend a trial of either a second anti-TNF agent or a biologic of an alternative mechanism of action[13].

The development of anti-TNFα inhibitors by the Kennedy Institute has had a major impact on the pharmaceutical industry. Sales of the five licensed anti-TNFα inhibitors (Key Patents: US App 08/446,674 / 20030064070A1; US App 20020136723A1; US App 20020010180A1) for all indications reached US$24.4 billion in 2011[14], most of which was used for the treatment of rheumatoid arthritis. Interest in the therapeutic use of biologics has blossomed since their discovery, with monoclonal antibodies making up around one-third of drugs in the sector, essentially all for chronic disease. High unit production costs of monoclonal antibodies are falling as their use grows. New products are now also being launched, including generic versions of the top selling antibodies as they lose patent protection, which should eventually benefit patients and society. It is predicted that by 2014, three of the four top drugs sold worldwide will be anti-TNFs[15], while the top 5 will be biologics, monoclonal antibodies and antibody like fusion proteins. This shows the outstanding impact of this research on the field of therapeutics[15].

Sources to corroborate the impact:

7. Lichtenstein, G. R., Bala, M., Han, C., DeWoody, K. & Schaible, T. Infliximab improves quality of life in patients with Crohn's disease. *Inflamm Bowel Dis* **8**, 237–243 (2002) DOI: 10.1097/00054725-200207000-00001 ***Paper reporting the impacts of anti-TNFα therapy on the quality of life of patients with Crohn's disease.***

8. van der Kooij, S.M. et al.Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis*. **68**:914-21 (2009). *doi:10.1136/ard.2008.092254* ***Paper reporting evidence that TNF treatment during early disease can result in drug-free remission.***

9. National Institute for Health and Clinical Excellence. Rheumatoid arthritis – etanercept and infliximab (**NICE technology appraisal guidance TA36**) issued 2002. http://guidance.nice.org.uk/TA36 [Accessed 2013] ***Original guidance endorsing the use***

of TNFα inhibitors in rheumatoid arthritis. This guidance has been superseded by Reference 11.

10. Taylor, P.C., Feldmann, M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. *Nat Rev Rheumatol* **5**:578-82 (2009). doi:10.1038/nrrheum.2009.181 ***Review reporting that the combination of an anti-TNFα agent with methotrexate remains the therapy of choice to reduce the signs and symptoms of rheumatoid arthritis.***

11. National Institute for Health and Clinical Excellence. [Guidance on TNF inhibitors in RA (TA130, TA186, TA195) issued 2007 and 2010] http://guidance.nice.org.uk/TA/WaveR/61 ***Current NICE technology appraisal guidance outlining the optimal use of biologics, and disease modifying antirheumatic drugs, for the management of rheumatoid arthritis.***

12. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years) (2009) http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/m/management_of_rheumatoid_arthritis_first_2_years.pdf. ***Updated clinical guidelines outlining the optimal use of biologics, and disease modifying antirheumatic drugs, for the management of rheumatoid arthritis.***

13. Smolen J.S. et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* **69**(6):964-975 (2010). doi: 10.1136/ard.2009.126532 ***Clinical guidelines for the management of rheumatoid arthritis, which recognise the importance of the early introduction of biologic TNFα inhibitors for patients failing to reach a treatment target of remission with DMARD drugs.***

14. R&D Pipeline News Apr 26 2012. Special Edn 1. Top 30 Biologics 2011. http://www.pipelinereview.com/index.php/2012042647751/FREE-Reports/TOP-30-Biologics-2011.html. (2013). ***Review outlining sales figures and commercial outcomes of the research.***

15. Merck Research Laboratories. Slide from Senior Vice President, MRL Franchise Head, Respiratory and Immunology. Email including data from EvaluatePharma received 27th June 2012 (available on request).