Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

A paradigm change in the treatment of multiple sclerosis

1. Summary of the impact

Researchers at the Dunn School of Pathology at the University of Oxford have played a major role in the development of an effective and innovative treatment for the chronic debilitating disease multiple sclerosis (MS). Research arising from the work of immunologists in Oxford, and partner neuroscientists in Cambridge University, has shown that low dose treatment with the lymphocyte depleting antibody alemtuzumab can break the cycle of disease in MS. Alemtuzumab acts by re-setting the immune system, leading to long-term arrest or remission, without increasing the risk of infection or malignancy. Large-scale studies since 2008 have shown that treatment is more effective and better tolerated than conventional forms of therapy. In June 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended that the drug be licensed for people with active relapsing-remitting MS. The research by Oxford University and its collaborators into the use of alemtuzumab in MS has been shown to benefit patients; it offers hope to millions of sufferers worldwide; and has had a major impact on the pharmaceutical industry.

2. Underpinning research

The autoimmune disease multiple sclerosis (MS) affects 2.5 million people worldwide and approximately 100,000 people between the ages of 20-40 years in the UK. This chronic disease follows a relapsing and remitting course during which the patient's own immune system attacks his or her nerve cells resulting in symptoms including numbness, tingling, blindness and even paralysis. Although some recovery may occur, the majority (65%) of patients relapse into a secondary progressive phase, which is punctuated with episodes of disease with incomplete recovery. 20% of patients have progressive illness from the start. The prognosis for individual patients is difficult to predict but the life expectancy for MS sufferers is 5-10 years lower than for the general population. There is no cure and conventional treatments such as IFNβ-1a (Rebif®) require frequent administration and are only moderately effective, reducing the relapse rate by only approximately 30%.

Research involving Oxford University immunologists at the Dunn School of Pathology has been pivotal in showing that the humanised anti-CD52 monoclonal antibody alemtuzumab is an effective treatment for MS. The Oxford University Immunology Group, led by Professors Herman Waldmann and Geoff Hale, showed that alemtuzumab targets and depletes the white blood cells (lymphocytes) damaging the nervous system in MS, whilst permitting reconstitution of the patients' immune system to protect against infection. In 1999 a clinical collaboration between the Oxford immunologists (who were also manufacturing the antibody) and a team at the University of Cambridge, led by neuroscientist Professor Alastair Compston, showed that alemtuzumab induced selective lymphocyte depletion in MS and reduced levels of the inflammatory mediators that contribute to the symptoms of disease[1]. Alemtuzumab was also shown to reduce both radiological and clinical inflammation of the central nervous system[1]. One consequence of this work was to highlight the intimate relationship between inflammation and demyelination of the nerve fibres, and the effect of inflammatory mediators on the exposed nerve fibres with the clinical course of MS. The important conclusion was made that treatment should be initiated as soon as possible to reduce inflammation[1].

The collaborators went on to conduct a clinical trial using short-term pulsed treatment with alemtuzumab in a larger group of MS patients. This confirmed suppression of the inflammatory

response and a reduction in the number of relapses, even after a single dose, and found a reduction in the disability of patients up to three years after treatment[2]. Both studies reinforced the early use of alemtuzumab to reduce the symptoms of MS. A subsequent study showed that following the use of alemtuzumab there is a differential recovery of the immune system with a preferential expansion of regulatory T cells (major players in preventing autoimmunity)[3]. Lymphocytes could be substantially depleted and then recovered, and the immune system re-set without incurring a risk of major infections.

3. References to the research

1. Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G, et al. (1999) Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Annals Neurology 46: 296–304. doi: 10.1002/1531-8249(199909)46:3<296::AID-ANA4>3.0.CO;2-# ***Results from a study on 27 MS patients showing improvement of MS symptoms with the use of alemtuzumab and providing insight into the mechanisms underlying MS.***

2. Coles AJ, Cox A, Le Page E, Jones J, Trip SA, Deans J, et al. (2006) The window of therapeutic opportunity in multiple sclerosis: Evidence from monoclonal antibody therapy. Journal of Neurology 253: 98–108. doi: 10.1007/s00415-005-0934-5 ***Report describing the improvements in MS following short-term pulsed courses of alemtuzumab. The authors proposed that the action of alemtuzumab resulted in the decrease of the inflammatory environment.***

3. Cox AL, Thompson SAJ, Jones JL, Robertson VH, Hale G, Waldmann H, et al. (2005) Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. European Journal Immunology 35: 3332–3342. doi: 10.1002/eji.200535075 ***This reference describes the modulation of the immune response in MS following alemtuzumab administration.***

Funding for research: This research has been supported since 1995 by Medical Research Council Programme Grants totalling £7.9M.

4. Details of the impact

Clinical impact

The use of Lemtrada (the proprietary name submitted to the health authorities for the use of alemtuzumab in the treatment of MS) is highly significant in terms of healthcare, because of the way it demonstrates that very short-term therapy can give long-term benefit in the treatment of immunological diseases.

Professors Waldmann and Hale acted as scientific advisors to the 2008 CAMMS223 trial (334 patients), which reported alemtuzumab to be superior as a treatment for MS than conventional interferon beta-1a (IFNβ-1a) therapy[4]. The significant improvement of results obtained in the study following short-term pulsed alemtuzumab treatment (given over 5 consecutive days in the first month and then over three days after 12 and 24 months) compared to IFNβ-1a administered over a three year period was confirmed in a subsequent retrospective study on the same group of patients over another two years[5].

Traditional MS treatments compromise the whole immune system risking the development of cancers and infections. In contrast, the controlled use of alemtuzumab in a short-term course of treatment achieves a long-term benefit for the patient with minimal side effects. Importantly, alemtuzumab therapy did not appear to result in the increased occurrence of malignancies. Indeed the repeated administration of alemtuzumab appeared to result in decreased adverse side effects[6]. These studies also highlighted the possibility that the suppression of inflammation in MS could inhibit those downstream disease mechanisms that lead to long-term disability. This is an extremely important factor for younger patients. Additional support for the efficacy of alemtuzumab

in MS was provided by recent results from the phase III clinical trial (MS-CARE II) comparing alemtuzumab with IFNβ-1a. This study, reporting efficacy and safety data from 840 treatment-failed and treatment-naive MS patients, described a decrease in disability with alemtuzumab with 65% patients relapse-free at two years (compared with 47% on IFNβ-1a), and a 49% and 42% reduction in relapse and disability rates respectively, compared to that obtained using IFNβ-1a (6). These improvements were durable despite the fact that 80% of patients received no further doses of alemtuzumab during the first year of the extension study[7].

The exceptional results of the phase III clinical trial have been included in an application for regulatory approval for use of Lemtrada in the USA and Europe[8]. This application is currently under review by the US Food and Drug Administration (FDA) – its use has already been unanimously supported by the FDA Advisory Committee. In June 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that the drug be licensed for people with active relapsing-remitting MS[9].

Financial impact

The 'blockbuster potential' valuation of Lemtrada was considered to have been a major factor in the acquisition of Genzyme by the pharmaceutical giant Sanofi in February 2011. Sanofi agreed to pay at least $20.1 billion and up to $23.9 billion, the exact amount to be paid depending on Genzyme achieving certain agreed milestones based principally on the development of Lemtrada. At that time the income from Lemtrada was predicted to be at least $700 million annually[10]. Genzyme is developing Lemtrada for use in MS in collaboration with BayerHealth[11].

5. Sources to corroborate the impact

4. Coles AJ, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. (2008) Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. New England Journal of Medicine 359: 1786–801. doi: 10.1056/NEJMoa0802670 ***Report of the pivotal international multicentre phase II randomised blind trial showing the efficacy of alemtuzumab compared to that obtained with conventional therapy for MS.***

5. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. (2012) Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 Clinical Trial. Neurology 78: 1069–1078. doi: 10.1212/WNL.0b013e31824e8ee7 ***Report on the large multicentre CAMMS223 trial in 334 patients reporting the increased efficacy of alemtuzumab compared to interferon β-1a after 5 years.***

6. Genzyme Corporation. Genzyme Announces Successful Phase III Results for Alemtuzumab (LEMTRADA(TM*)) in Multiple Sclerosis. 2011. Available from: http://www.businesswire.com/news/genzyme/20111113005072/en ***Report on the successful phase III results of the MS-CARE II trial.***

7. Genzyme Corporation. Effect of Genzyme's LEMTRADA™ Maintained in Patients Beyond Two-Year Pivotal MS Studies 2013. Available from: http://genzyme.newshq.businesswire.com/press-release/effect-genzymes-lemtrada-maintained-patients-beyond-two-year-pivotal-ms-studies ***Report dated 21st March 2013 describing the continuance of improved health in MS patients treated with Lemtrada despite no further treatment in the first year of the extension period in the MS-CARE II trial.***

8. Genzyme Corporation. Genzyme's LEMTRADA™ (alemtuzumab) Application for MS Accepted for Review by the FDA 2013. Available from: http://genzyme.newshq.businesswire.com/press-release/genzymes-lemtrada-alemtuzumab-application-ms-accepted-review-fda ***Bid for US and Europe regulatory approval for Lemtrada.***

9. European Medicines Agency. Lemtrada. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003718/sm

ops/Positive/human_smop_000544.jsp&mid=WC0b01ac058001d127 ***Webpage confirming that on 27 June 2013 the CHMP recommended the granting of a marketing authorisation for Lemtrada.***

10. Samedan Ltd Pharmaceutical Publishers. Blockbuster Takeover. Samedan Ltd 2011. Available from: http://www.samedanltd.com/magazine/12/issue/151/article/2913 ***Website stating income predicted by Sanofi-Aventis and Genzyme for Lemtrada.***

11. LaMotta L. Genzyme And Bayer Make A Deal. Forbes 2009. Available from: http://www.forbes.com/2009/03/31/genzyme-bayer-campath-markets-equity-healthcare.html ***Website reporting the link between Genzyme and BayerHealthcare.***