Institution: University of Cambridge

Unit of Assessment: 4

Title of case study:
Alemtuzumab: a highly effective treatment for multiple sclerosis

Period when the underpinning research was undertaken: 2008 - 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor David Alastair Compston	Professor of Neurology Director of Research	Jan 2004 – Sep 2015 Oct 2015 – Sep 2018
Professor Alasdair Coles	Genzyme Professor of Neuroimmunology	Apr 2004 - present

Period when the claimed impact occurred: 2014 - present

Is this case study continued from a case study submitted in 2014? N

1. **Summary of the impact (indicative maximum 100 words)**

Multiple sclerosis (MS) is an autoimmune disease that affects the brain and spinal cord. An estimated 2,500,000 people in the world have multiple sclerosis (MS Trust); it affects >100,000 people in the UK and is the commonest neurological cause of disability in adults. Compston and Coles' research led to the drug alemtuzumab being used by more than 24,000 people in over 70 countries, leading to reduced accumulation of disability and lower risk of developing progressive MS. This in turn allows more people to stay in work, with a higher quality of life, requiring lower drug and healthcare costs. The drug has also had significant commercial impact, generating more than EUR 1.859 billion in net sales.

2. **Underpinning research (indicative maximum 500 words)**

Background
In the autoimmune disease multiple sclerosis, the body's own immune cells attack and destroy myelin, the covering of nerves, in the brain and spinal cord. This means electrical signals fail to travel down the nerves, causing a wide range of symptoms that can be severely debilitating. These span fatigue, muscle weakness, impaired mobility, reduced vision, bowel problems and more. Initially these occur as distinct attacks that recover in the "relapsing-remitting" phase of the disease, which is followed in most cases by the "secondary progressive" phase where people experience continuous worsening of their disability.

There is currently no cure for multiple sclerosis, but there are several drugs that reduce inflammation and therefore reduce the attack rate and accumulation of disability. Alemtuzumab, developed by University of Cambridge researchers, is one of the most effective and cost-effective of these.

Developing Alemtuzumab for the treatment of multiple sclerosis
Alemtuzumab, previously known as Campath-1H, was made in the Cambridge University laboratories of Cesar Milstein, Herman Waldmann and Greg Winter. Targeting the lymphocytes, a subgroup of the white cells of the immune system, this was the first monoclonal antibody to be used as a therapy in humans. From 1991 to 2013, Alastair Compston (now retired) and Alasdair Coles developed this drug as a treatment for multiple sclerosis. The key research since 2000 includes three clinical trials, all led by Alasdair Coles:

one phase 2 trial in 2008 [1] and two phase 3 trials in 2012 [2]. All three showed that alemtuzumab was superior to the standard treatment of the day: interferon beta 1a. In particular, alemtuzumab prevented people from getting more disabled from their MS, and even led to most people experiencing an improvement in their disability.

Investigating the risks and benefits of Alemtuzumab

From 2013, Alasdair Coles and colleagues published research that allowed doctors and people with multiple sclerosis to better understand the benefits and risks of alemtuzumab. Their studies showed that alemtuzumab is more effective than standard treatment at reducing the brain damage caused by MS, seen on MRI scans [3]; confirmed that patients' disability improved after alemtuzumab [4]; and that it remains effective for at least five years [5].

Importantly, treated patients have the greatest experience of the long-term benefit of alemtuzumab and have reported this in several ways (Alasdair Coles led on the 6-year extension of the pivotal trials and his team also contributed data from the Cambridge cohort to international databases on real-life experience of multiple sclerosis drug treatment. From these, it is now even clearer that both alemtuzumab (and another monoclonal antibody, natalizumab) are more effective than all other MS drug treatments [6]. They have also published widely on the side-effects of alemtuzumab, both the common treatable thyroid disease and the much rarer, more serious side effects of blood clotting problems and kidney disease.

In 2019 Coles and colleagues showed - for the first time - that early treatment with alemtuzumab reduces the risk of transitioning from the relapsing-remitting to the progressive phase of multiple sclerosis [7].

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

Evidence of 2* research quality: Research is published in peer-review journals. Research was supported by competitively won grants

1. **Coles AJ**, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K, Tandon PK (CAMMS223 Trial Investigators). Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *New England Journal Medicine* 2008; 359(17):1786-801 *
2. **Coles AJ,** […], Compston DA; for the CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; 380(9856):1829-39 *
3. Arnold DL, Fisher E, Brinar VV, Cohen JA, **Coles AJ**, […], Compston DA; CARE-MS I and CARE-MS II Investigators. Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon β-1a in MS. *Neurology* 2016;87(14):1464-1472. PubMed PMID: 27590291; PubMed Central PMCID: PMC5075976. Open Access repository Univ of Cambridge
4. Giovannoni G, Cohen JA, **Coles AJ**, […] , Compston DA; CARE-MS II Investigators. Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. *Neurology*. 2016;87(19):1985-1992. PubMed PMID: 27733571; PubMed Central PMCID: PMC5109953 *
5. **Coles AJ**, Cohen JA, […], Arnold DL; CARE-MS II and CAMMS03409 Investigators. Alemtuzumab CARE-MS II 5-year follow-up: Efficacy and safety findings. *Neurology* 2017; 89(11):1117-1126. doi: 10.1212/WNL.0000000000004354. Epub 2017 Aug 23. PubMed PMID: 28835403; PubMed Central PMCID: PMC5595276 *
6. Kalincik T, Brown JW, […], **Coles A**; MSBase Study Group.. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. *Lancet Neurol* 2017;16(4):271-281. doi: 10.1016/S1474-4422(17)30007-8. [Epub ahead of print] PubMed PMID: 28209331 *
7. Brown JWL, **Coles A,** […], Robertson N, MSBase Study Group. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA* 2019;321(2):175-187. doi: 10.1001/jama.2018.20588. PubMed PMID: 30644981 *

*These publications have been peer reviewed.

Competitive funding received
Sanofi and Bayer HealthCare Pharmaceuticals
NIHR Cambridge Biomedical Research
2012-2017 MRC; PI: Coles; Developmental Clinical Studies - new use of a licensed drug in preventing autoimmunity after alemtuzumab treatment of MS GBP965,058
2008-11 Multiple Sclerosis Society of Great Britain & Northern Ireland GBP137,326;
2011-18 Keratinocyte growth factor: promoting thymic reconstitution and preventing autoimmunity after alemtuzumab Moulton Charitable Trust. GBP305,298
2012-17 Developmental clinical studies - preventing autoimmunity after alemtuzumab treatment of MS, from the Medical Research Council (with Joanne Jones as co-applicant).
2012. Does early treatment prevent progression? Long term follow-up of alemtuzumab patients. Multiple Sclerosis Society GBP92,613
2020 Centre of Excellence Grant [Co-PI with Ragnhildur Thora Karadottir] Combatting progression in MS - when and how? Multiple Sclerosis Society GBP1,850,000

4. Details of the impact (indicative maximum 750 words)
An estimated 2,500,000 people in the world have multiple sclerosis (MS Trust), which affects >100,000 people in the UK and is the commonest neurological cause of disability in adults. University of Cambridge research has led to the following impacts:

Impact on policy/guidelines
In 2014, Coles provided evidence and gave expert advice during the NICE alemtuzumab approval process [A]. Chief Executive Sir Andrew Dillon said, “We are very pleased to be able to recommend alemtuzumab for adults with relapsing-remitting multiple sclerosis. Evidence has shown that alemtuzumab is more effective and less expensive than current similar treatments for those with severe relapsing-remitting MS. The NICE Committee heard from clinical specialists and patients during the appraisal process who described alemtuzumab as a revolutionary treatment for some people, allowing them to live their lives as they had before their diagnosis” [B].

Alemtuzumab is now prominent in national treatment guidelines for multiple sclerosis in the UK, including the Association of British Neurologists guidance (listed as a high-efficacy drug under recommendations for starting disease-modifying treatment), the NHS England treatment algorithm, the European Committee for Research and Treatment of Multiple Sclerosis and the European Academy of Neurology guideline and the American Academy of Neurology Practice [C].

In 2019 new safety concerns about alemtuzumab emerged, and the European Medicines Agency temporarily restricted the use of alemtuzumab pending a review. Coles advised Sanofi and gave evidence to the Committee for Medicinal Products for Human Use in December 2019, following which the restrictions were lifted. The new recommended guidance was issued in February 2020 for safe use of alemtuzumab [D]

Impact on health
If multiple sclerosis is not treated, or lower efficacy drugs are used, most patients accumulate disability. However, treatment with alemtuzumab can lead to disability improvement. Data from the latest extension of the pivotal trials (n=c.800, reported at the 2019 European Committee for Treatment and Research in Multiple Sclerosis meeting) shows that nine years after starting alemtuzumab, 49% of patients have improved disability [2].

The most important outcome for people with multiple sclerosis is prevention of the secondary progressive phase of the disease, which occurs 15-25 years after disease onset. Cambridge research showed that first-line treatment with alemtuzumab lowers the risk of developing secondary progressive disease over 8 years from 41%, if untreated, to 21%. Of patients treated with alemtuzumab or two other powerful drugs (fingolimod, natalizumab), 16% had entered the secondary progressive phase at 9 years, compared to 27% on

interferon-beta. Therefore, of the approximately 25,000 patients currently treated with alemtuzumab, 2,750 people will have been prevented from developing secondary progressive multiple sclerosis, compared to standard treatment. In accord with this, quality of life measures improve with alemtuzumab treatment of multiple sclerosis (see below) [E].

Alemtuzumab is very convenient for patients, who require five daily infusions at baseline and three daily infusions a year later. Over the eight years since its use in patient treatment, approximately half of the 369 patients originally enrolled in trials have required no further treatment [F]. There are potentially serious side-effects of alemtuzumab, but most can be managed safely.

As of November 2019, over 25,000 people with MS have been treated with alemtuzumab [Sanofi] and the drug is licensed and reimbursed over 70 countries worldwide [G]. The greatest use is in Europe and Northern America (as these are the regions with the highest incidence of multiple sclerosis). The UK is the highest prescribing country of alemtuzumab, *pro rata*.

Commercial impact/impact on economy

In 2012 Campath was acquired by Sanofi, a global pharmaceutical company. In September 2013, alemtuzumab was licensed in the UK since when it has been licensed in over 70 countries, including the EU and United States [F]. Since licensing, annual sales of alemtuzumab have steadily increased, generating net sales income between 1st January 2014 and 31st December 2019 of EUR1.859 billion [H].

Alemtuzumab, and the other high efficacy drugs, double the chance of improvements in amount of work, work attendance and work productivity by people with multiple sclerosis [I]. Alemtuzumab is an expensive drug, but because it is given so infrequently and has such a prolonged action, its cost compares favourably to drugs of a similar class. In Austria, alemtuzumab use saves EUR 60-100,000 in drug costs per person treated over ten years. In the US, between USD 450-600,000 is saved for each person treated over 20 years [J].

In 2014, NICE judged that alemtuzumab was the most cost-effective treatment for MS compared with other available immunosuppressant drugs, giving incremental cost gain - of GBP13,600 - 24,500 per quality-adjusted life year (QALY) compared with glatiramer acetate and GBP8,900 per QALY compared with fingolimod, both alternative MS treatments[A]. The Norwegian Institute of Public Health found that “over a 20-year time horizon, alemtuzumab dominated all other alternative treatments, i.e. it was both more effective and less costly” [J]; the same conclusion was reached by Hamidi et al [J]. In Italy, over the lifetime of someone with multiple sclerosis, alemtuzumab is more cost effective than similar drugs and also leads to an incremental benefit of 1 QALY per person [J]. Finally, a similar study in the US showed lower cost and higher QALY gains from alemtuzumab, compared to any other MS drug [J].

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

A. NICE: Final appraisal determination *‘Alemtuzumab for treating relapsing–remitting multiple sclerosis’*. Issued March 2014. pages 47, 61
B. Fierce Pharma: NICE recommends new treatment option for patients with MS (2014) May 28, 2014
C. National guidelines recommending use of alemtuzumab: **(i)** Association of British Neurologists (2015) Guidance on disease modifying therapies for adults with multiple sclerosis. Published in Practical Neurology: page 4
(ii) NHS England algorithm for MS treatments (2018): pages 6-10
(iii) European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN). Guidelines 2017. Published in the Multiple Sclerosis Journal in 2018: page 12

(iv) American Academy of Neurology Practice guideline recommendations 2018: Disease modifying therapies for adults with multiple sclerosis. Published in Neurology online on April 23, 2018: pages 5-7
D. Lemtrada (alemtuzumab) Drug Safety Update volume 13, issue 7: February 2020: 2.
E. González RA, Kita M, Crayton H, Havrdova E, Margolin DH, Lake SL and Giovannoni G. Alemtuzumab improves quality-of-life outcomes compared with subcutaneous interferon beta-1a in patients with active relapsing-remitting multiple sclerosis. Multiple Sclerosis Journal 2017. 23(10): 1367-1376:
F. Sanofi 8-Year Data on Lemtrada® (Alemtuzumab). page 2
G. Email correspondence with Sanofi Genzyme
H. Sanofi annual reports 2015 – 2019. Coversheet contains collated sales figures and links to sources by year 2015(page 92); 2016 report (page 95); 2017 (page 92); 2018 (page 91); 2019 (page 64)
I. Chen J, Taylor BV, Blizzard L, Simpson Jr S, Palmer AJ, van der Mei IAF. Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data. Journal of Neurology, *Neurosurgery & Psychiatry* 2018;89:1200-1207. doi:10.1136/jnnp-2018-318228
J. International health economics analysis of alemtuzumab:
(i) Walter E, Berger T, Bajer-Kornek B, Deisenhammer F. Cost-utility analysis of alemtuzumab in comparison with interferon beta, fingolimod, and natalizumab treatment for relapsing-remitting multiple sclerosis in Austria. *Journal of Medical Economics* 2019*;* 22:3, 226-237, DOI: 10.1080/13696998.2018.1556668 page 2
(ii) Couto E, Hamidi V, Ringerike T, Odgaard-Jensen J, Harboe I, Klemp M. Medicines Used for Multiple Sclerosis – A Health Technology Assessment. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2016 Feb. page 81
(iii) Hamidi V, Couto E, Ringerike T, Klemp M. A Multiple Treatment Comparison of Eleven Disease-Modifying Drugs Used for Multiple Sclerosis. *J Clin Med Res*. 2018;10(2):88-105. doi: 10.14740/jocmr3168w. Epub 2017 Dec 30. PubMed PMID: 29317954; page 98
(iv) Stanisic S, Bertolotto A, Berto P, Di Procolo P, Morawski The cost-effectiveness of alemtuzumab in the management of relapse-remitting multiple sclerosis in Italy. Global & Regional Health Technology Assessment 2019; page 11
(v) Sawad AB, Seoane-Vazquez E, Rodriguez-Monguio R, Turkistani F. Cost-effectiveness of different strategies for treatment relapsing-remitting multiple sclerosis. J Comp Eff Res. 2017 Mar;6(2):97-108. doi: 10.2217/cer-2016-0056. Epub 2017 Jan 25.