CASE REPORT

Timing is everything in the treatment of multiple sclerosis

Claire Louise McCarthy,¹ Gavin Giovannoni,² Alasdair John Coles³¹Department of Clinical Neurosciences, Addenbrooke's Hospital, Cambridge, UK²Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK³Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Correspondence to

Professor Alasdair John Coles, ajc1020@medschl.cam.ac.uk

Accepted 19 March 2015

SUMMARY

We present two similar cases of relapsing–remitting multiple sclerosis, both of whom received treatment with the monoclonal antibody alemtuzumab, but had significantly different long-term outcomes. Patient A is 12 years into his illness and was treated early in his disease course, he has no disability and continues to perform at a high level as a professional golfer. Patient B was initially started on interferon- β 1a therapy and went on to have two disabling relapses on this treatment which resulted in a degree of fixed disability prior to the start of alemtuzumab. 10 years into his disease course he has moderate disability and daily symptoms of spasticity in his legs which impair his quality of life. These two contrasting cases highlight the difficult decision of when to start potent immune modulating therapies for multiple sclerosis in young adults who appear well early in their disease but have the potential to rapidly accrue irreversible disability from future relapses.

BACKGROUND

Multiple sclerosis is a common, unpredictable neurological disease which may cause severe disability in young adults. With a peak age of onset of 20–30 years it has a huge impact on patients' social and professional lives. Multiple sclerosis is widely believed to be an autoimmune disease characterised by plaques of inflammation in the central nervous system. Neurologists are now in the fortunate position of having numerous treatment options for relapsing–remitting multiple sclerosis which range in their potency and side effect profile. The question of when to initiate potentially toxic therapies in young adults, who are early in their disease course but may accrue irreversible disability from future relapses, can be challenging.

Alemtuzumab is a lymphocyte depleting monoclonal antibody that has been pioneered as a treatment for multiple sclerosis in Cambridge, UK, since 1991. Large phase II and III trials in relapsing–remitting multiple sclerosis have shown it to be highly efficacious in reducing relapses and the accumulation of disability compared with interferon β 1a.^{1–3} Studies also suggest that in order to prevent accumulation of disability, alemtuzumab needs to be administered early in the disease course.⁴ We present two patients, with similar initial presentations of relapsing–remitting multiple sclerosis, who received alemtuzumab at different time points in their disease. These cases effectively highlight the potential immense personal cost of delaying treatment for individuals.

CASE PRESENTATION

Patient A was first seen in the research clinic in Cambridge in 2004 for consideration of the phase II alemtuzumab trials. He was 47-years old, a professional golfer and was married with two children. Prior to the onset of his multiple sclerosis he was well and he took no medications. He was a smoker of 20 cigarettes/day and drank no alcohol. His first attack of multiple sclerosis was in September 2002 when he developed dense sensory loss in his left arm, trunk and leg which persisted for 5 weeks, suggestive of an episode of cervical spine demyelination. Except for mild residual numbness in the left hand he made a near full recovery following 3 days of IV methylprednisolone. He had an MRI of the brain showing multiple T2 high-signal lesions in the periventricular and deep white matter. His second clinical episode of demyelination occurred in July 2003 when he developed poor co-ordination, fatigue, reduced walking distance and memory problems. He had to suspend his golf tournament schedule and his symptoms slowly resolved over the course of 2 months. He had a second MRI of the brain which showed new demyelinating lesions.

He was eligible for the phase II trial of alemtuzumab versus interferon β 1a and was randomised to alemtuzumab. He received his first treatment in June 2004 (20 months after the onset of his disease) with the second annual dose in June 2005. He remained well and had no further relapses. He experienced a few, brief episodes of his previous left hand numbness (maximum duration 30 min) for 1 week in May 2009 in the context of a hot environment (a 'Uhthoff phenomenon' which does not indicate new disease activity). He has remained relapse free since receiving only two courses of alemtuzumab treatment and his MRI of the brain from 2010 to Oct 2013 showed no new demyelinating lesions and showed partial resolution of old lesions. When reviewed recently in clinic his neurological examination was normal and he continued to play professional golf to a high standard.

Patient B had his first attack of multiple sclerosis in 2004. At this time he was 39-years old, married with two young children and was leading a busy professional life. He was a non-smoker, drank no alcohol and exercised regularly. His only significant medical history was of glandular fever as a teenager and the excision of a thyroglossal cyst. He was on no regular medication. His first episode in March 2004 was a spinal cord attack resulting in sensory loss in his right upper limb, trunk and legs, from which he recovered over several months with only a mild residual deficit in sensation in his right

CrossMark

To cite: McCarthy CL, Giovannoni G, Coles AJ. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208960

hand. His second attack, a year later, resulted in a spastic paraparesis and temporary use of a wheelchair. He had a prompt response to a course of oral steroids and was left with Lhermitte's symptom, a sensory band at T8 and mild leg stiffness. His MRI of the brain and spine confirmed the clinical diagnosis of relapsing–remitting multiple sclerosis. On his first visit to the research clinic at Cambridge in 2005 he brought this insightful statement of his views:

I have no interest in starting any of the current immune-suppressing drugs as they offer limited effectiveness in reducing attacks, have shown limited effectiveness at slowing progression of disease and have some nasty side effects. I recognise that Campath-1H (alemtuzumab) can result in some very serious side effects (e.g. Graves' disease) but the possibility of halting this disease (and possibly recovering some deficits) is currently not offered by any other treatments. This disease has already robbed me of a substantial number of things and I would be more than happy to take the risks which accompany Campath-1H to regain some of these.

Unfortunately recruitment for the phase II alemtuzumab trial had completed and so, after discussions with a second neurologist, he started interferon β 1a therapy in February 2006. However, he subsequently went on to have two disabling relapses in the following 5 months which required him to use a stick to walk 100 m, giving him an Expanded Disability Status Scale (EDSS) score of 6.0. At this point he was eligible for a new open-label study of alemtuzumab which tested the hypothesis that giving a non-cell binding alemtuzumab variant ('SM3') prior to alemtuzumab treatment would induce tolerance and reduce the development of anti-alemtuzumab antibodies. Prior to receiving his first alemtuzumab treatment in November 2006 (32 months after disease onset) he had made a partial recovery from his latest relapse and had moderate disability (EDSS 3.5).

He subsequently remained relapse free and went on to have his second scheduled course of alemtuzumab in November 2007. His MRI of the brain in 2008 showed no new demyelinating lesions. In 2009, he developed Graves' disease and was treated with carbimazole and subsequently radioactive iodine. In addition, he experienced thoracic shingles. Both are established adverse effects of alemtuzumab. He has remained relapse free for the past 8 years following alemtuzumab with no new disease activity on serial MRI of the brain and spine. He does, however, continue to have the moderate disability that he had prior to starting the alemtuzumab (last EDSS 3.5). He experiences ongoing symptomatic spasticity in his legs and intermittent periods of recurrence of his old symptoms particularly on exertion. He remains in full-time employment but is exploring the option of early retirement on medical grounds as he finds the commute and long hours physically demanding.

DISCUSSION

Alemtuzumab has received National Institute for Clinical Excellence (NICE) approval for use in the UK and in November 2014 was approved by the US Food and Drug Administration (FDA). Alemtuzumab is a highly effective treatment for relapsing–remitting multiple sclerosis with a reduction in relapse rate of 49–74%^{1–3} and reduction in disability accumulation by 42–71% compared with interferon β 1a.^{1–3} Patients require regular blood monitoring following treatment due to the risk of developing autoimmune disorders, namely thyroid disorders (30% of patients) and immune thrombocytopenia (1–3% of patients).

We describe two cases of multiple sclerosis treated with alemtuzumab. When the first was treated in a phase II clinical trial, he was not disabled and had just experienced two relapses with less than 2 years of disease duration; his professional sporting career has continued to flourish. In contrast, the second patient was first treated with interferon β 1a for 8 months, during which he experienced two relapses, and eventually received alemtuzumab 32 months after disease onset and after having accumulated significant disability; he is contemplating early retirement from a sedentary profession. These different outcomes illustrate the cost of 'escalating' therapy strategies, where patients may acquire fixed disability from relapses while on partially effective treatments before receiving more potent therapies.

Clearly conclusions cannot be drawn by simply comparing two similar cases, however, data from clinical trials of alemtuzumab support the view we advanced in 2005 that there is a 'window of therapeutic opportunity' early in the course of multiple sclerosis, to optimise the long-term benefits of potent immunotherapies.⁴ The phase II and phase III trial demonstrated a significant reduction in disability over 2–3 years of 71% and 42%, respectively, in the alemtuzumab group, compared with the interferon β 1a group.^{1–3} One phase III trial, CARE-MS1, did not show a significant reduction in disability but the authors attributed this to an unexpectedly low relapse rate in the interferon β 1a group.² Our longer term experience with alemtuzumab in Cambridge, over a median of 7 years, has shown that 59/87 (68%) of patients had an improved or unchanged disability score compared with baseline.⁵ Data from the 5-year follow-up of the phase II trial patients estimates that 72% patients receiving alemtuzumab were relapse-free versus 41% of patients receiving interferon β 1a.⁶ Longer disease duration at the time of treatment was associated with a trend towards worse outcome in both the phase II alemtuzumab trial⁶ and our open-label series.⁵

Neurologists are now in the fortunate position of having a choice of treatments for multiple sclerosis which range in their clinical effectiveness and side effect profile. The potential risk of adverse events with a particular drug treatment needs to be carefully weighed against the benefit of effective disease control early in the disease. These two cases effectively highlight the high personal cost of delaying treatment for individual patients.

Learning points

- ▶ Multiple sclerosis is a leading cause of disability in young adults.
- ▶ Alemtuzumab is a highly effective treatment for relapsing–remitting multiple sclerosis with a significant reduction in both relapse rate and accumulation of disability in comparison to interferon β 1a.
- ▶ These two cases highlight the high personal cost of delaying treatment for individual patients. The risks of serious side effects from treatment need to be balanced against the lifelong effects of fixed disability from inadequate disease control.

Contributors CLM wrote the paper and was an investigator on both trials in which the patients were treated. AJC reviewed and edited the manuscript. He was the principle investigator on both trials in which these patients were treated. GG reviewed the manuscript. He previously treated both patients.

Competing interests AJC has received consulting and lecture fees from Genzyme, lecture fees from Merck Serono, and research support paid to his institution from Genzyme.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Coles AJ, Compston DA, Selmaj KW, *et al.* Alemtuzumab vs interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008;359:1786–801.
- 2 Cohen JA, Coles AJ, Arnold DL, *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819–28.
- 3 Coles AJ, Twyman CL, Arnold DL, *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012;380:1829–39.
- 4 Coles AJ, Cox A, Le Page E, *et al.* The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J Neurol* 2006;253:98–108.
- 5 Tuohy O, Costelloe L, Hill-Cawthorne G, *et al.* Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 2015;86:208–15.
- 6 Coles AJ, Fox E, Vladic A, *et al.* Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012;78:1069–78.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow