Alemtuzumab in multiple sclerosis: latest evidence and clinical prospects

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Abstract: Alemtuzumab was first used in multiple sclerosis in 1991. It is a monoclonal antibody which is directed against CD52, a protein of unknown function on lymphocytes. Alemtuzumab causes a lymphopenia, following which homeostatic reconstitution leads to prolonged alteration of the immune repertoire. This reduces the risk of relapse and disability accumulation in multiple sclerosis; it is the only drug to show superiority over interferon β -1a in disability outcomes in a monotherapy phase III trial. It should be used with a parallel risk management programme to identify the principal adverse effects of alemtuzumab, especially secondary autoimmunity months or years later, mainly against the thyroid but also immune thrombocytopenia. This review charts the development of alemtuzumab as a drug for multiple sclerosis and summarizes the latest clinical trial data.

Keywords: alemtuzumab, autoimmunity, monoclonal antibodies, multiple sclerosis

Introduction

After the seminal discovery of the technology for generating monoclonal antibodies [Kohler and Milstein, 1975] monoclonal antibodies were developed to target T-cell subsets *in vivo* [Cobbold *et al.* 1984]. A family of antibodies that could bind to CD52 was identified from a single inoculation of a rat with human lymphocytes. From this, a set of rat antibodies was isolated which could selectively kill human lymphocytes with human complement. The immunoglobulin M (IgM) antibody from this group was selected, as it was the most effective at binding human complement, and named the ‘Cambridge Pathology 1’ or ‘Campath-1’ antibody [Hale *et al.* 1983].

Campath-1 was used to purge allogeneic bone marrow transplants of T cells [Waldmann *et al.* 1984] but it could not debulk leukaemic cells despite their ability to fix complement *in vitro* [Dyer *et al.* 1989]. So a variant antibody was sought that could lyse by antibody-dependent cytotoxicity. This led to the discovery of Campath-1G, a monoclonal antibody of the IgG2b isotype that could clear leukaemic cells from blood [Dyer *et al.* 1989]. However, this rodent antibody was limited in its use by its immunogenicity, so a humanized form, Campath-1H, was then manufactured to clinical grade for therapeutic use [Riechmann *et al.* 1988].

Campath-1H, now known as alemtuzumab, is a monoclonal antibody directed against CD52. Although the function of CD52 is unknown [Xia *et al.* 1991] it is present on a number of cell populations, including thymocytes, B and T lymphocytes and monocytes but not on plasma cells or haematological precursors [Gilleece and Dexter 1993]. It also shows differential expression on various cells of the adaptive immune system and spares the innate immune system [Rao *et al.* 2012; Clark *et al.* 2012].

Therapeutic uses of alemtuzumab

Campath-1H was licensed as a treatment of fludarabine-resistant B-cell chronic lymphocytic leukaemia in 2001 [Keating *et al.* 2002]. It has also been used off label in the treatment of several autoimmune haematological diseases, such as autoimmune haemolytic anaemia, pure red cell aplasia, aplastic anaemia, immune thrombocytopenic purpura [Waldmann and Hale, 2005] and as part of the conditioning regimen in patients about to have haematopoietic stem cell transplants [Gomez-Almaguer *et al.* 2012]. From the 1980s it has also been used in organ transplantation as an induction agent, but also with the aim of avoiding or reducing maintenance immunosuppression [Weissenbacher *et al.* 2010].

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From the 1980s, the late Martin Lockwood began to investigate the use of Campath-1H in vasculitis. Campath-1H was used in the setting of refractory and relapsing antineutrophil cytoplasmic antibody associated vasculitis. From 1991 to 1999, 71 patients were treated, with 10 patients managing to achieve long-term remission for more than 3 years. However, the majority of patients did have relapsing disease, and adverse events, especially infections, were common in this group of systemically compromised patients with multiple prior immunotherapies. Campath-1H shows some efficacy in Behcet's disease, a small vessel vasculitis [Lockwood *et al.* 2003].

From 1990, discussions between Hermann Waldmann and Alastair Compston began about the possible use of alemtuzumab in multiple sclerosis. This led to the first trials of the drug in progressive multiple sclerosis [Waldmann and Hale 2005].

First use of alemtuzumab in progressive multiple sclerosis

In 1991, the first patient with multiple sclerosis was treated using alemtuzumab. Six more patients were treated by 1993 [Moreau *et al.* 1994] and by 1999 a total of 36 patients, all with progressive multiple sclerosis, received treatment [Coles *et al.* 1999b]. These 36 patients had mean disease duration of 11 years with a mean Expanded Disability Status Scale (EDSS) score of 6.5 and 0.7 relapses per year. Their disability had worsened by at least 1 EDSS point over the previous year.

Treatment with alemtuzumab (given as a 20 mg daily intravenous infusion over 4 h for 5 days) in this patient population was associated with a very significant reduction in gadolinium-enhanced magnetic resonance imaging (MRI) lesions, maximally by over 90% for at least 18 months after a single pulse of treatment. This correlated with a significant reduction in relapses, even greater than the expected decline in relapses in a progressive multiple sclerosis patient population, as the mean relapse rate fell to 0.02 per year representing a 97% reduction in relapse rate. This was evidence that lymphocyte depletion by alemtuzumab could directly affect the inflammation seen in multiple sclerosis [Coles *et al.* 1999a].

Unfortunately, this did not lead to a clinical improvement in the disability in these patients. In fact, their disability worsened with time at a rate

of 0.02 EDSS points for each patient each year. Evidence for continued neurodegeneration in these patients was shown by progressive cerebral atrophy on follow-up MRI scanning. This particular group of patients who showed continuing disease progression had the highest inflammatory load prior to commencing alemtuzumab therapy. This group of patients were followed up with MRI scanning many years later (14 years post treatment) and did not demonstrate any increase in lesion load but did demonstrate further cerebral atrophy [Coles *et al.* 2006]. This was reflected in their EDSS score, the median being 7.5 (range 4.5–9) at latest follow up [Hill-Cawthorne *et al.* 2012].

This experience of treating progressive multiple sclerosis with alemtuzumab led to the hypothesis that immunotherapies might be more beneficial if given early in the course of the relapsing–remitting phase.

First use of alemtuzumab in relapsing–remitting multiple sclerosis

The first use of alemtuzumab in relapsing–remitting multiple sclerosis was in an open-label pilot study of 22 patients. These patients had disease that had failed to respond to standard disease-modifying therapy or they had a high relapse rate early in the course of the disease, indicating a poor prognosis. Disease duration had a mean of 2.7 years in this patient group, with an annualized mean relapse rate of 2.21 per year (with an annualized relapse rate of 2.94 in the year prior to treatment). In the year before treatment their EDSS score had increased by a mean of 2.2 EDSS points (range 0–7.5). After alemtuzumab, the mean relapse rate fell to 0.19/patient/year, giving a 91% reduction in relapse rate. Mean EDSS scores fell by 1.4 points in this patient group, with 16/22 patients having had an improvement in their disability by 1 year [Coles *et al.* 2006].

Experience from other open-label studies also demonstrated the efficacy of alemtuzumab in active disease. Hirst and colleagues administered alemtuzumab to a group of 39 patients with aggressive relapsing multiple sclerosis. The mean follow-up period was 1.89 years with the annualized relapse rate falling by 92% and a 0.36 EDSS point score improvement [Hirst *et al.* 2008].

In a study of 45 patients with aggressive relapsing multiple sclerosis, who continued to have relapsing disease despite interferon therapy over a follow-up

period of 2 years, Fox and colleagues showed that treatment with alemtuzumab reduced the annualized relapse rate by 94%, with a mean improvement of 0.38 points on the EDSS score [Fox *et al.* 2012].

From this early experience of the contrasting effects of alemtuzumab on progressive or early relapsing–remitting multiple sclerosis, it was concluded that there is a ‘window of opportunity’ early in the disease course when inflammation is the dominant process driving multiple sclerosis. However, subsequent neurodegenerative mechanisms (most likely influenced by the prior inflammatory events) come into play during progressive multiple sclerosis, causing the subsequent increase in disability that is unresponsive to immunotherapies. This formulation led to the unique designs of the phase II and phase III trials, in which patient selection was limited to people with short disease histories and limited disability.

Phase II and III trials of alemtuzumab

The industry-sponsored phase II and III trials of alemtuzumab began with the phase II International Campath-1H in Multiple Sclerosis (CAMMS 223) trial and then the subsequent phase III trials: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis I and II (CARE-MSI and CARE-MSII) [Cohen *et al.* 2012; Coles *et al.* 2012].

The trials of alemtuzumab used some key principles:

- (1) Patients recruited had early disease without significant disability. In the phase II CAMMS 223 trial, disease duration was limited to 3 years with an EDSS of less than 3.0. In the phase III trials, CARE-MSI and CARE-MSII, the EDSS was extended to less than 3.0 and less than 5.0 respectively, with disease durations extended to 5 and 10 years.
- (2) Patients should have active disease. In practical terms, this meant two relapses in the last 2 years (with at least one relapse in the previous 12 months). In the phase II trial, a gadolinium-enhanced lesion also needed to be present on one of four pretreatment MRI scans.
- (3) Alemtuzumab should be compared with an active drug rather than just placebo. At the time the trials were set up, the active drugs available were the interferons and

glatiramer acetate, so alemtuzumab was compared against perhaps the most efficacious of these, subcutaneous interferon β -1a.

- (4) Disability should be used as the primary endpoint. This was measured as increase in EDSS of 1 EDSS point sustained on repeat testing at least over 6 months.
- (5) Alemtuzumab should be tested as either a first-line therapy (CAMMS223 and CARE-MSI) or in patients with active disease on one of the first-line drugs (either interferons or glatiramer acetate) (CARE-MSII), the latter being a group at increased risk of accumulating fixed disability [Rudick *et al.* 2004; Prosperini *et al.* 2009; Rudick and Polman, 2009].

The first conclusion from these trials is that alemtuzumab reduces relapse rate compared with interferon β -1a: in the phase II trial by 69% [Coles *et al.* 2012] and in the phase III trials, CARE-MSI and CARE-MSII, by 55% and 49% respectively.

The second conclusion is that alemtuzumab reduces accumulation of disability compared with interferon β -1a. The evidence for this is not as strong as for relapse rates. In the phase II and CARE-MSII trials alemtuzumab significantly reduced the number of patients who acquired fixed disability during the trial compared with interferon β -1a. However, in the CARE-MSI trial there was no statistically significant difference, perhaps because the study was inadvertently underpowered by the unexpectedly low rate of only 11% of patients in the interferon β -1a group meeting the disability outcome. (The study had been powered on the expectation from prior experience that 20% of the interferon β -1a cohort would acquire disability.)

The third conclusion is that alemtuzumab did not only reduce the number of patients accruing fixed disability, but mean disability improved in alemtuzumab patients over 3 years for the CAMMS 223 trial and 2 years for the CARE-MSII trial. This new endpoint of ‘sustained reduction in disability’ was a fall in EDSS of at least one point, confirmed at 6 months [Coles *et al.* 2011].

Side effects of alemtuzumab

Infusion-related cytokine release syndrome

Administration of alemtuzumab is associated with an infusion cytokine release syndrome [Moreau

et al. 1996]. The symptoms experienced by patients include headache, rash and flu-like symptoms. Occasionally, patients also get a recurrence of their multiple sclerosis symptoms which is transient. The cytokines released are tumour necrosis factor α and interferon γ followed by interleukin (IL)-6. The cytokine release syndrome can be ameliorated by prior administration of methylprednisolone with use of an antihistamine and paracetamol.

Infection

Despite the lymphopenia induced by alemtuzumab, only increases in mild-to-moderate infections are seen, such as upper respiratory tract infections and urinary tract infections. Serious infections such as progressive multifocal leukoencephalopathy and pneumocystis jiroveci pneumonia have not been seen [Coles *et al.* 2012]. Other infections that have been seen (single cases only) are spirochaetal gingivitis, pyogenic granuloma and *Listeria* meningitis. As a result of the *Listeria* infection, patients are now given dietary advice when taking alemtuzumab.

Malignancy

Malignancy has not been more frequent in the alemtuzumab group in the trials [Coles *et al.* 2012]. However, it has also been recognized that the trials were not powered in such a way as to show events of small frequency that could be attributed to alemtuzumab. There have been three cases in the phase III trials of papillary thyroid cancer. These cancers were detected by ultrasound scanning in the workup of thyroid autoimmunity due to alemtuzumab. Studies suggest that incidence of thyroid cancer in patients with Grave's disease is 3–4% [Kraimps *et al.* 2000; Kim *et al.* 2004]. One study suggests monitoring of these patients will identify incidental cancers [Berker *et al.* 2011]. One patient from the extension study of the phase II trial died from non-Epstein–Barr virus associated Burkitt's lymphoma [Coles *et al.* 2012]. This is a rare tumour associated with patients who are immunocompromised, so may have been caused by alemtuzumab.

Autoimmunity

The main adverse effect of alemtuzumab is secondary autoimmunity. This has been reported in other states when there is lymphocyte reconstitution after a profound lymphopenia [Hsiao *et al.* 2001; Gilquin *et al.* 1998]. Most commonly, 30% of patients after alemtuzumab develop autoimmune thyroid disease,

both Graves' disease and hypothyroidism. Although the predilection for the thyroid gland is unexplained, it may be that patients with multiple sclerosis have an inherited susceptibility to autoimmune thyroid disease. There is an increased incidence of Graves' disease in family members of patients with multiple sclerosis [Broadley *et al.* 2000].

Immune thrombocytopenic purpura (ITP) occurs in 1–3% of patients receiving alemtuzumab. The death of the first patient with this complication from a brain haemorrhage led to a temporary dose suspension of alemtuzumab and the establishment of a risk management programme consisting of informing patients about warning signs when they might have a low platelet count (e.g. easy bruising) and monthly blood tests to check their platelet counts. Patients with ITP subsequently identified in this programme have been managed with steroids, intravenous immunoglobulin and, in some, rituximab. All patients are now well with normal platelet counts off treatment.

Other autoimmune diseases have occurred in lower frequencies after alemtuzumab, most notably antglomerular basement membrane disease [Clatworthy *et al.* 2008]. There have been three reported cases in total, two of which needed renal transplantation. The third case has stable renal function off treatment. There have also been single cases of autoimmune haemolytic anaemia and autoimmune neutropenia.

We have reviewed autoimmunity after alemtuzumab in detail elsewhere [Costelloe *et al.* 2012]. Briefly, following observations in the nonobese diabetic (NOD) mouse [King *et al.* 2004] we have identified pretreatment levels of serum IL-21 as potential biomarkers [Jones *et al.* 2009].

Conclusion

At present alemtuzumab is an unlicensed therapy for multiple sclerosis. It is currently under consideration for a license in Europe and the USA. Over one phase II and two phase III trials, it has demonstrated clear efficacy in relapse reduction, and in improving disability outcomes, over interferon β -1a. A question for physicians is, what place does alemtuzumab have in the multiple sclerosis treatment spectrum? There is no consensus to date between an escalation or induction strategy. An 'escalation' strategy would be to withhold alemtuzumab until the patient's disease has clearly failed to respond to one or two of the other

disease-modifying therapies, to mitigate the risks of alemtuzumab, but denying them the benefits of early treatment. Alternatively, alemtuzumab could be used as 'induction' therapy (i.e. first-line treatment), to achieve rapid control of disease activity early in its natural history, to be followed by pulsed alemtuzumab or even other disease-modifying therapies. With further work on IL-21, it may be possible in the future to put patients into 'high'- and 'low'-risk groups for the development of autoimmunity after alemtuzumab, which will aid the decision process for patients. The licensing authorities will determine the details of the risk management programme; undoubtedly, though, alemtuzumab should only be used by centres familiar with its safety profile, and with systems in place to monitor for thyroid disease (3 monthly), ITP (monthly) and other autoimmunity for at least 5 years after each dosing with alemtuzumab.

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Conflict of interest statement

Dr Coles serves on advisory boards for Multiple Sclerosis Society of GB and NI, Genzyme Corporation, and Merck Serono; has received funding for travel from Merck Serono, Bayer Schering Pharma, UCB, and Genzyme Corporation; serves as the Co-Editor of *Advances in Clinical Neuroscience and Rehabilitation*; holds a patent for the use of IL-21 as a biomarker for autoimmunity after alemtuzumab; serves as a consultant for Genzyme Corporation and Merck Serono; and his department has received research support from Genzyme Corporation and UCB-Celltech.

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