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REVIEW

Alemtuzumab Therapy for Multiple Sclerosis

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Abstract Alemtuzumab is a humanized monoclonal antibody that is administered daily for 5 days, and then no further therapy is required for 12 months. It causes rapid and prolonged lymphocyte depletion; the consequent homeostatic reconstitution leads to a radically reformed lymphocyte pool with a relative increase in regulatory T cells and expansion of autoreactive T cells. Although previously licensed for the treatment of B-cell chronic lymphocytic leukemia, it is now been considered for licensing in the treatment of multiple sclerosis (MS). From a disappointing experience with alemtuzumab in progressive MS, Alastair Compston and I argued that immunotherapies should be given early in the course of the disease. In a unique program of drug development in MS, alemtuzumab has been compared in 1 phase 2 trial and 2 phase 3 trials with the active comparator interferon beta-1a. In all trials, alemtuzumab was more effective in suppressing relapses than interferon beta-1a. In one phase 2 and one phase 3 trial, alemtuzumab also reduced the risk of accumulating disability compared with interferon beta-1a. Indeed, alemtuzumab treatment led to an improvement in disability and a reduction in cerebral atrophy. The safety issues are infusion-associated reactions largely controlled by methylprednisolone, antihistamines, and antipyretics; mild-to-moderate infections (with 3 opportunistic infections from the open-label experience: 1 case each of spirochaetal gingivitis, pyogenic granuloma, and Listeria meningitis); and autoimmunity. Usually autoimmunity is directed against the thyroid gland, but causes (1 %) immune thrombocytopenia, and in a few cases antiglomerular basement membrane syndrome. Alemtuzumab is an effective therapy for early relapsing-remitting MS, offering disability improvement at least to 5 years after treatment. Its use requires careful monitoring so that potentially serious side effects can be treated early and effectively.

Keywords Multiple sclerosis · Alemtuzumab · Antibody · Disability · Autoimmunity

Introduction

Alemtuzumab was originally known as Campath-1H because it was the first monoclonal antibody to be made in the University of Cambridge Pathology Department and it was humanized. This was made possible by the Cambridge inventions for producing and humanizing monoclonal antibodies [1, 2]. Although alemtuzumab was originally intended for the treatment of leukemias [3], it was soon tested for autoimmune disease [4–9], and was first used in multiple sclerosis (MS) in 1991.

Alemtuzumab's Mechanism of Action

Alemtuzumab is given as an intravenous infusion of 12 mg/day for 5 consecutive days in the first cycle and 3 consecutive days in the second cycle. Subsequent cycles are not given electively, but are given in response to a return of disease activity.

Alemtuzumab binds to CD52, a 12-amino acid cell surface protein of unknown function [10–12] that is expressed at high levels on T cells and B cells and at lower levels on monocytes, macrophages, and eosinophils with little found on Natural Killer cells, neutrophils, and hematological stem cells. Cells of the innate immune system are unaffected. Although monocytes carry the CD52 antigen, they are depleted for only a few days. Within minutes of infusing a single dose of alemtuzumab

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in humans, peripheral lymphocytes are depleted, probably by antibody-dependent, cell-mediated cytotoxicity [13]. Cross-linking of Natural Killer cells causes a rise in serum cytokines, including tumor necrosis factor-α, interleukin-6, and interferon-γ [14], which results in infusion-associated symptoms that are successfully reduced or prevented by pre-treatment with corticosteroids and an antihistamine [15].

The therapeutic effect of alemtuzumab is mediated by the remolding of the immune repertoire that accompanies homeostatic lymphocyte reconstitution. Recovery of B- and T-lymphocytes to the lower limit of normal after a single course of alemtuzumab takes 8 months and 3 years, respectively [16]. For the first 6 months after treatment, there is a predominance of memory T-cell number cells, especially those with a regulatory phenotype (CD4+ CD25hi FoxP3+), with reduced constitutive cytokine expression [17]. During this time, the B-cell compartment is largely naïve and memory B cells are slow to return [18].

Alemtuzumab Treatment of Progressive MS

The first group of patients to be treated with alemtuzumab in 1991-93, were 36 patients with the progressive disease for a duration of 11 years, a mean Expanded Disability Status Scale (EDSS) score of 6.5 and an average of 0.7 relapses per year, whose disability had worsened by ≥1 EDSS point in the preceding year [19]. After alemtuzumab, the mean relapse rate fell to 0.02 per annum, representing a 97 % reduction and new magnetic resonance imaging lesion formation was also demonstrated to be reduced by 90 %. However, the disability of the group of patients continued to deteriorate, just as their cerebral atrophy progressed. At the latest follow-up, a median of 14-years post-treatment, the median disability of the cohort had worsened to an EDSS of 7.5 (range, 4.5-9) [16].

Alemtuzumab Treatment of Relapsing-Remitting MS Disease

Open-Label Trials

The second group of patients to be treated with alemtuzumab had relapsing-remitting MS, with a mean relapse rate of 2.2, which fell after alemtuzumab to 0.14 (equaling a 94 % reduction). This time, unlike the progressive cohort previously discussed, mean disability scores fell after alemtuzumab (by a mean of 1.2 points at 2 years).

This experience led us to conclude that disability accumulation early in MS is driven by inflammation and that anti-inflammatory treatments are effective if given early in the course of the disease [20]. From this analysis, our suggestion emerged that there is a "window of therapeutic opportunity" for immunotherapies in MS [21].

Controlled Trials of Alemtuzumab

A phase 2 trial was published, and the headline results from 2 phase 3 trials have been presented but not yet published (Alasdair Coles at European Committee for the Treatment of MS 2011 for the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis trials (CRE-MS) I and of Jeff Cohen at the American Association of Neurology in 2012 for CARE-MS II). All trials have been rater-blinded; the first dose effect of alemtuzumab precludes double-blinding.

After the hypothesis of the "window of therapeutic opportunity," patients recruited to these trials were selected on the basis of a limited disease duration (restricted to <3 years in phase 2, 5 in CARE-MS I, and 10 in CARE-MS II); low disability (Expanded Disability Status Score <3 in phase 2 and CARE MSI, and <5 in CAREMSII), but high disease activity (at least 2 relapses in the preceding 2 years) (Table 1). In each trial, alemtuzumab was compared with the active drug interferon beta-1a. In phase 2 and CARE-MS I, alemtuzumab was tested as a first-line therapy. In CARE-MS II, participants had already experienced at least 1 relapse on disease-modifying therapy.

These trials (summarized in Table 2) show that alemtuzumab reduces the relapse rate more effectively than interferon beta-1a. In the phase 2 trial and CARE-MS II, alemtuzumab also reduced the number of patients who acquired sustained accumulation of disability during the trial; indeed, mean disability of alemtuzumab-treated patients actually improved. In CARE-MS I, fewer alemtuzumab-treated patients accumulated disability than those on interferon beta-1a, but this difference was not statistically significant. This trial was inadvertently underpowered because only 11 % of interferon beta-1a patients met the disability endpoint, rather than the expected 20 %. An extension of the phase 2 trial showed sustained superiority of alemtuzumab in comparison with interferon beta-1a for a 5-year duration [22].

Safety

Infusion-Associated Symptoms

An infusion reaction is common at the time of alemtuzumab treatment, with a rash, headache, influenza-like symptoms and less frequently transient recurrence of previous MS symptoms (Table 3). Pre-treatment with corticosteroids, an antihistamine, and paracetemol minimizes these symptoms.

Infections

In all trials, mild-to-moderate infections, especially of the respiratory and urinary tracts, were more frequent among patients receiving alemtuzumab than those receiving interferon beta-1a (Table 3). Serious infections were rare (e.g., occurring

Table 1 Baseline Characteristics of Patients in Clinical Trial Phases 2 and 3

	Phase 2 CAMMS 223* N=333	Phase 3 CARE-MS I N=581	Phase 3 CARE-MS II* N=637
Mean age in years (SD)	32.3 (8.5)	33.0 (8.2)	35.1 (8.6)
Gender (% Female)	64.3	64.7	66.9
Mean EDSS score (SD)	2.0 (0.7)	2.0 (0.8)	2.7 (1.2)
Median disease duration in years (range)	1.3 (0.1-6.3)	1.7 (0.1-6.0)	3.8 (0.2-16.9)
Mean no. relapses in past 2 years (range)	2.3 (1-7)	2.4 (1-7)	2.7 (1-9)

CAMMS = Campath in Multiple Sclerosis; EDDS = Expanded Disability Status Scale; MS = Multiple Sclerosis

*Only including patients on the 12 mg/kg alemtuzumab arm

in 4 % of patients after alemtuzumab in the CARE MS II trial compared with 1.5 % using interferon beta-1a). Three patients in an open-label experience had opportunistic infections from which they fully recovered (1 case each of spirochaetal gingivitis, pyogenic granuloma, and Listeria meningitis).

Malignancy

Cancers have not been statistically more frequent after alemtuzumab than interferon beta-1a in any of the trials (Table 3), but these studies were not powered to pick up differences in low-frequency events. In the phase 3 trials, there were 3 cases of thyroid papillary carcinoma. These were all detected as a result of thyroid ultrasound scanning of patients with biochemical thyroid dysfunction in which context papillary carcinomas are recognized as "incidental" [23]. In the extension of the phase 2 trial, 1 patient died from non-EBV associated Burkitt's lymphoma, and another patient who received alemtuzumab developed Castleman's disease, a pre-lymphomatous condition, and is now in remission after R-CHOP (rituximab, cyclophosphamide, doxyrubicin, prednisolone) [24].

Autoimmunity

The principal adverse effect of alemtuzumab is novel autoimmunity arising months to years after treatment (Table 3). The thyroid gland is the most common target, being affected in 20 to 30 % of patients, most frequently with the development of Grave's disease. The first person to manifest immune thrombocytopenia died of a brain hemorrhage. Then a careful risk management program was put in place with education for patients and monthly blood counts. This has led to the identification and treatment of all subsequent cases before any significant bleeding events could occur. Most patients have required corticosteroids, and a number of patients had intravenous immunoglobulin, along with some who had rituximab. All of these patients are now well, most are off the treatment and have normal platelet counts.

Table 2 Efficacy of Alemtuzumab

	Phase 2 CAMMS 223* N=223 >3 years	Phase 3 CARE-MS I N=581 >2 years	Phase 3 CARE-MS II* N=637 >2 years
Relapse rate			
Relapse rate reduction	69 %†	55 %‡	49.4 %‡
Annualized relapse rate (alem vs IFNb)	0.10 vs 0.36	0.18 vs 0.39	0.26 vs 0.52
Proportion relapse free (alem vs IFNb)	77 % vs 52 %†	78 % vs 59 %‡	65 % vs 47 %‡
% of patients with sustained accumulation of disability at 6 months	7 % vs 26 %†	8 % vs 11 % Not significant	13 % vs 21 %†
Change in mean EDSS from baseline	Improvement of 0.39 compared with deterioration of 0.38 on IFNb1a†	No significant change	Improvement of 0.17 compared with deterioration of 0.24 on IFNb1a‡
Hazard ratio of patients with sustained reduction in disability	Not assessed	No significant change	2.57 (1.57, 4.2)†

Alem = alemtuzumab; CAMMS = Campath in Multiple Sclerosis; EDDS = Expanded Disability Status Scale; MS = Multiple Sclerosis

*Only reporting the results of the 12 mg/kg arm; † $p<0.01$; ‡ $p<0.0001$

Table 3 Safety Profile of Alemtuzumab

	Phase 2 CAMMS 223* N=333 >3 years	Phase 3 CARE-MS I N=581 >2 years	Phase 3 CARE-MS II* N=637 >2 years
Deaths	1 due to ITP 1 due to myocardial infarct	1 due to motor accident	1 due to motor accident; 1 due to aspiration pneumonia
Infusion-associated symptoms	98 %	90 %	92 %
Infections			
All	66 % Mild-to-moderate (47 % on IFNb)	67 % Mild-to-moderate (46 % on IFNb)	79 % Mild-to-moderate (66 % on IFNb)
Life-threatening	0	0	0
Autoimmunity			
Thyroid	26 %	18 %	17 %
ITP	0.9 %	0.8 %	1 %
Goodpasture's syndrome	0	1 case on extended follow-up	0
Neoplasia (alem vs IFNb)	2.8 % vs 0.9 %	0.5 % vs 0	0.6 % vs 1.5 %
Details	1 colon cancer after IFNb-1a, 1 cervical cancer, 1 breast cancer, and 1 non–EBV-associated Burkitt's lymphoma in patients receiving the 24-mg dose of alem	2 cases of papillary thyroid cancer after alem	1 basal cell carcinoma on IFNb and 1 on alem, 1 thyroid and 1 parathyroid tumor after alem 1 acute myeloid leukemia on IFNb-1a

Alem = alemtuzumab; CAMMS = Campath in Multiple Sclerosis; IFNb-1a = interferon beta-1-alpha; ITP = immune thrombocytopenia; MS = Multiple Sclerosis

*Only reporting the results of the 12 mg/kg arm

Other autoimmune diseases have occurred at lower frequency after alemtuzumab. There have been 3 cases of Goodpasture's disease detected among several thousand people who received alemtuzumab for MS, both in trials (1) and off-label (2); in 2 of the cases, renal transplantation was required, and the remaining cases had stable renal function off treatment. These have been reported several times in the literature [21, 25]. There have also been single cases of autoimmune neutropenia and autoimmune hemolytic anemia.

Autoimmunity is a recognized phenomenon of reconstitution from lymphopenia in a variety of different conditions [26, 27]. We have shown that pre-treatment serum interleukin-21 may serve as a biomarker for the risk of developing autoimmunity for months to years [28].

Immunogenicity

Despite being humanized, alemtuzumab induces anti-alemtuzumab binding and neutralizing antibodies in as much as 30 to 70 % of patients 1 month after the first and second cycles, respectively. However, because the interval between treatment cycles is at least 1 year, such antibodies usually become undetectable before the next cycle [24]. If persistent, neutralizing antibodies become problematic in patients who have received multiple alemtuzumab cycles. We have shown that pre-treatment with an altered version of alemtuzumab, which no longer binds to its target, can effectively induce tolerance to alemtuzumab itself [24].

Discussion

Alemtuzumab is an exploratory treatment for relapsing-remitting MS and is being considered for licensing in the United States and Europe in 2013. A unique development program has tested alemtuzumab with an active comparator in people with early disease in 1 phase 2 and 2 phase 3 trials. In each trial, alemtuzumab offers clinical efficacy superiority in comparison with interferon beta-1a. However, it has potentially serious adverse effects, particularly autoimmune diseases for months or years after alemtuzumab. These require careful monitoring and a high degree of vigilance from patient and physician alike to institute timely therapy. The details of monitoring are currently being reviewed by regulatory authorities, but these are likely to include monthly platelet monitoring and 3 monthly thyroid function monitoring for some years after alemtuzumab treatment.

Several issues involving alemtuzumab treatment of MS remains to be investigated. As an effective treatment with significant adverse effects, opinions vary as to whether alemtuzumab should be considered a "second-line" therapy or if it should be used as a first-line therapy instead. Although,

undoubtedly, alemtuzumab has more safety concerns than current first-line therapies, some patients and physicians may feel that this it is a reasonable cost for the superior efficacy of alemtuzumab in this context. After the first 2 annual cycles, it is unclear how subsequent cycles of therapy should be planned. Options include a fixed schedule of re-treatment, re-treatment only with no disease activity or re-treatment with drugs, such as interferon beta in an "induction" program. The long-term safety profile of alemtuzumab, particularly for low frequency events, needs to be established.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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