Alemtuzumab – A New Efficacy Benchmark in Relapsing–Remitting Multiple Sclerosis?

Omar A Khan

Professor of Neurology and Director, Multiple Sclerosis Clinical Research Center and Image Analysis Laboratory, Department of Neurology, Wayne State University School of Medicine

Abstract

The disease-modifying drugs (DMDs) available for the treatment of multiple sclerosis (MS) have been used effectively for nearly two decades. These treatments delay the neurorodegenerative process, but do not restore lost neurological function. New oral DMDs are becoming available that offer improved convenience over existing injectable DMDs. Recently, several monoclonal antibody treatments have been developed for MS; the furthest developed is alemtuzumab (Campath-1H). In a landmark phase II clinical trial (CAMMS223) on patients with relapsing–remitting MS (RRMS), short cycles of alemtuzumab given at the start, at 12 months and optionally at 24 months, demonstrated superior and sustained efficacy in terms of relapse rates and magnetic resonance imaging (MRI) findings over the comparator compound, interferon beta-1a (IFNβ-1a), which was given subcutaneously and continuously. Most notably, the mean disability score for patients receiving alemtuzumab showed an unprecedented improvement, whereas for IFNβ-1a it deteriorated. Alemtuzumab in treating RRMS is the subject of two ongoing phase III trials, the results of which have the potential to change future treatments and prognoses for many patients.

Keywords

Alemtuzumab, monoclonal antibody, multiple sclerosis, disease-modifying drugs, disability, clinical trials

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Correspondence: Omar A Khan, Multiple Sclerosis Center and MR Image Analysis Laboratory, Department of Neurology, Wayne State University School of Medicine, 4201 St Antoine, 8D-UHC, Detroit, MI 48201, US. E: okhan@med.wayne.edu

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The introduction of disease-modifying drugs (DMDs) during the 1990s made chronic therapies that inhibit the disease process in multiple sclerosis (MS) available to patients for the first time.[1,2] While the currently available DMDs decrease the number of relapses, delay the onset of disabilities, improve quality of life (QoL) and allow increased participation in work and social activities,[3–7] they only modestly delay disease progression and none has the capacity to restore lost neurological function. Therefore, improvement in motor and cognitive ability in MS has remained a substantially unmet clinical need. This deficiency has prompted the search for and development of better alternatives, some of which are now pending regulatory approval. The treatment landscape in MS treatment will soon see a rapid transition; many promising new DMDs are currently in development, including a number of oral medications and parenteral monoclonal antibodies (mAbs). The arrival of these new treatments will profoundly increase the number of options available to the neurologist and may change the prognosis for many patients with MS. This article will outline the currently available MS treatments and consider the potential benefits of investigative agents. It will then focus on the fully humanised mAb: alemtuzumab (Genzyme). The clinical development programme of this drug, its potential lymphocyte modulatory role, its potential advantages over existing injection-based, newer oral therapies and investigative agents will also be discussed.

Current Treatments for Relapsing–Remitting Multiple Sclerosis

Eight DMDs have been approved for the treatment of MS: interferon beta-1a ([IFNβ-1a], Rebif® subcutaneously [SC] and Avonex® intramuscular [IM]), IFNβ-1b (Betaseron® SC and Extavia® SC), glatiramer acetate (Copaxone® SC), natalizumab (intravenous [IV] infusion humanised monoclonal antibody against the α4 subunit of α4β1 integrin on leukocytes, Tysabri®), mitoxantrone (an immune suppressor and antineoplastic, Novantrone® IV infusion) and fingolimod (a sphingosine 1-phosphate receptor [S1PR] modulator, Gilenya®, an oral capsule that was approved by the US Food and Drug Administration [FDA] in September 2010). Various clinical trials conducted over the past 20 years have investigated the efficacy, safety and tolerability of these medications.[8–19]

Recent head-to-head trials comparing different IFNβs and comparing IFNβs with glatiramer acetate have shown comparative efficacy between the products.[20–23] However, one study demonstrated that IFNβ-1a SC was significantly more effective than IFNβ-1a IM in reducing relapse rate and activity on magnetic resonance imaging (MRI) and increasing time to relapse.[24,25] Another study, the Independent Comparison of Interferon (INCOMIN) trial, also showed superiority of IFNβ-1b SC during two years of treatment over IFNβ-1a IM in terms of the proportion who were relapse-free, the relative risk of relapse and

Table 1: Disease-modifying Drugs in Development for the Treatment of Multiple Sclerosis

Treatment Type	Indication, Administration Method and Dose	Phase II or III Clinical Trial Efficacy Data		Major Safety/Tolerability Concerns in Clinical Trials
		Patient Inclusion Criteria EDSS Score and n-values	% Relapse Reduction	
Alemtuzumab (MabCampath®)	In development for RRMS. 12mg per day IV injection, for 5 days at month 0 and 12mg per day IV for 3 days at month 12	EDSS 0–3 Alemtuzumab pooled (n=222) IFNβ-1a (n=111)	74 (p<0.001)*	Association with infusion-related cytokine release syndrome leading to fever, rash and chills during the infusion, autoimmunity and development of immune thrombocytopenic purpura. Autoimmune thyroid-associated events were increased with alemtuzumab. Single case of glomerular basement membrane disease.[62]
Rituximab	In development for RRMS. 1,000mg infusions of rituximab on days 0 and 15	EDSS 0–5 Rituximab (n=69) Placebo (n=35)	20 (p=0.04)	Infusion-associated adverse events such as chills, nausea, pruritus, pharyngolaryngeal pain, urinary tract infection, sinusitis.[75]
Daclizumab	In development for RRMS 2mg/2 weeks (high dose), 1mg/4 weeks (low dose)	EDSS 0–5 IFNβ + placebo (n=77) IFNβ + low-dose daclizumab (n=78) IFNβ + high-dose daclizumab (n=75)	43 and 32** (p=0.18 and 0.31)	Similar incidence of adverse events for daclizumab with or without IFNβ. With daclizumab greater incidence of nausea, urinary tract infection and upper respiratory tract infection.[76]
Cladribine (Mylinax®)	In development for CIS and RRMS. Oral tablet up to 3.5mg/kg 1 x week for 4 weeks	EDSS 0–5.5 Cladribine 3.5mg/kg (n=433) Placebo (n=437)	58 (p<0.001)	Lymphopenia, headache, nasopharyngitis.[47] Serious adverse events in patients receiving cladribine included infections (herpes zoster) and neoplasms (5 cases of benign uterine leiomyoma, and cases of melanoma, carcinoma of the pancreas, ovary and cervix [*in situ*]).
BG-12 (dimethyl fumarate)	In development for RRMS. Oral tablet 120 or 240mg 3 x per day	EDSS 0–5 BG-12 720mg (n=63) Placebo (n=65)	32 (p<0.272)	Most common adverse events were: flushing, MS relapse and headache. Adverse events significantly more frequent with BG-12 than placebo included: abdominal pain, flushing, hot flush, headache, fatigue and feeling hot. Serious adverse events more frequent with BG-12 were MS relapse, abdominal pain, pelvic inflammatory disease, phlebitis and urinary retention.[48]
Laquinimod	In development for RRMS. Oral tablet 0.6mg/daily	EDSS 1–5 Laquinimod (n=106) Placebo (n=102)	32 (p=0.0978)	Transient and dose-dependent increases in liver enzymes.[45]
Teriflunomide	In development for RRMS. Oral tablet, 7mg, 14mg once daily	EDSS ≤5.5 + ≥1 relapse in previous year or at ≥2 relapses in previous 2 years 1,088 patients randomised 1:1:1 to teriflunomide 7mg, 14mg or placebo	For 7 and 14mg: 31.2%, 31.5% risk reduction (p=0.0002 and p=0.0005)	No difference between teriflunomide 7mg, 14mg and placebo in serious hepatic disorders (2.5, 1.9, 2.5%), ALT >3 x ULN (6.7, 6.3, 6.7%) or serious infections or infestations (2.2, 1.6 and 2.5%) for placebo, 7 and 14mg groups.[50]

**p-value for difference versus placebo or versus active comparator. **% differences are for daclizumab high-dose with interferon beta (IFNβ) versus IFNβ with daclizumab low-dose versus IFNβ with placebo.*
ALT = alanine transaminase; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; IV = intravenous; RRMS = relapsing–remitting multiple sclerosis; ULN = upper limit of normal.

the proportion remaining free from new T2 lesions detected by MRI.[26] A disadvantage with IFNβ therapy in some patients is the development of neutralising antibodies and this is associated with reduced efficacy,[27–32] particularly in patients with persistently high titres of antibodies. Such patients often benefit from switching to a non-IFNβ therapy.[33]

For patients who relapse despite using IFNβs or glatiramer acetate, the next treatment options are natalizumab or mitoxantrone. Both natalizumab and mitoxantrone can be highly effective in treating refractory cases of relapsing MS, but mitoxantrone is decreasingly used.[14,15,34,35] However, both of these drugs are associated with serious adverse events (AE) and therefore are generally used as second-line options, although use as first-line therapy may be warranted in selected cases.[14,15,36,37] Evaluation of pooled clinical trial data has shown that, compared with placebo, approximately 0.1% of patients treated with natalizumab for 18 months developed the rare but potentially

Table 2: Alemtuzumab Mechanism of Action and Autoimmunity Studies

Mechanism of Action Study	Study Methods	Study Findings	Reference
Genetics, T-cell apoptosis IL-21 levels in RRMS patients treated with alemtuzumab	T-cell apoptosis, serum IL-21 and genetic studies determined in groups from a population of 232 patients with RRMS	IL-21 expression is genetically pre-determined. Greater levels of T-cell apoptosis, T-cell cycling and serum IL-21 in patients who develop autoimmunity after alemtuzumab treatment. High IL-21 levels may facilitate autoimmunity	Jones et al. 2009[68]
B-cell reconstitution after alemtuzumab treatment	B-cell levels and serum BAFF (measured in 78 patients with RRMS receiving alemtuzumab and 13 healthy controls)	B-cell reconstitution is rapid after alemtuzumab, levels return to baseline by 3 months. BAFF levels elevated for 12 months. Most abundant cell types 1 month after treatment: immature transitional 1 B cells. High BAFF levels may have a role in autoimmunity	Thompson et al. 2010[60]
Transgenic human CD52 mouse model	Transgenic mouse model expressing human CD52 to study effect of alemtuzumab on immune function	Alemtuzumab transiently increased serum cytokines and reduced blood lymphocytes similar to human response. Lymphocyte depletion was lower in lymphoid organs. Eliminating natural killer cells and neutrophils reduced effects of alemtuzumab; removal of complement factor had no effect – alemtuzumab is believed to mediate lymphocyte depletion primarily through ADCC versus complement cytotoxicity	Hu et al. 2009[58]

ADCC = antibody-dependent cell-mediated cytotoxicity; BAFF = B-cell activating factor; IL = interleukin; RRMS = relapsing–remitting multiple sclerosis.

fatal progressive multifocal leukoencephalopathy (PML),[38] and this risk increases with time on the drug. Post-marketing data indicate a similar risk, with 11 reported cases of PML in 18,000 patients receiving at least 18 months of therapy.[2] More recent data indicate a global incidence of 1.63 PML cases per 1,000 patients treated.[39] Mitoxantrone is associated with cardiotoxicity; in one analysis of 1,378 patients with no history of congestive heart failure (CHF), the risk of CHF in patients with MS was <0.20% (mean cumulative dose of mitoxantrone 60.5mg/m^2). In the same study, 2.2% of patients experienced an asymptomatic reduction in left ventricular ejection fraction of <50%, although this was not correlated with cumulative mitoxantrone dose.[40] Furthermore, the risk of developing mitoxantrone-therapy-related acute leukaemia was 0.74% in one retrospective study,[41] which is much higher than the rate observed in clinical studies.[40]

With the exception of the recently approved oral medication, fingolimod, the other approved DMDs for use in MS require regular administration (daily, every other day, weekly or monthly [in the case of natalizumab]) by injection for indefinite periods to allow optimal outcomes.[42] Injection anxiety and injection-site reactions can discourage patients resulting in low adherence, particularly during the first few months of treatment, leading to suboptimal health outcomes.[42–44] In addition, some patients may have difficulty following the correct dosing regimen or injection technique.[43] Finally, a lack of perceived efficacy is the main reason for discontinuation of therapy despite the fact that some therapies require longer courses to show health benefits.[43]

New Treatment Options for Relapsing–Remitting Multiple Sclerosis are Being Developed

Recently, a series of oral DMDs have entered late-stage development: cladribine, dimethyl fumarate, laquinimod and teriflunomide. Data from phase II and III trials suggest that these have similar or improved efficacy compared with existing DMDs, although properly designed head-to-head comparative studies are lacking. However, the option of an oral therapy and the elimination of injections could represent an attractive option to MS patients.[2,18,42,45–49] The approval of oral DMDs may improve patient adherence to therapy, particularly for patients who have concerns with frequent injections. One such treatment, teriflonomide, has been shown in a recently completed phase III trial to have a benign safety profile, similar to that of placebo.[50] However, most other oral DMDs have been shown to have significant side effects such as increased rates of malignancy and infections and these may outweigh the benefits for some patients.[42] In addition to these oral preparations, there are a number of mAbs undergoing phase II and III trials for the treatment of MS, including rituximab (anti-CD20 on B-lymphocytes), daclizumab (anti-CD25 on T cells), alemtuzumab (anti-CD52 on both T and B cells), ofatumumab and ocrelizumab (newer anti-CD-20 types).[51] See *Table 1* for an overview of the efficacies of novel treatments relative to placebo or active comparator. Of these, alemtuzumab is the furthest developed and has been used in the most extensive clinical trials of these agents in MS therapy. Alemtuzumab is already approved for first-line treatment of B-cell chronic lymphocytic leukaemia.[52] In early studies, alemtuzumab has shown remarkable efficacy in the treatment of MS, with significant improvements in disability. Alemtuzumab is administered in short courses at 12-month intervals, making dosing regimens entirely different from the available injectable DMDs.[53,54]

Mode of Action of Alemtuzumab

Alemtuzumab is a humanised mAb that targets CD52, a glycoprotein on the surface of various blood cell types (T- and B-lymphocytes, monocytes and eosinophils).[55] CD52 antigens are expressed at high density on T- and B-lymphocytes but at lower density on cells of the innate immune system and not on haematological precursor cells.[53,56] Once bound to CD52, alemtuzumab triggers antibody-mediated cytotoxicity and complement fixation;[57] subsequent lymphocyte depletion and cytokine induction appear to be mediated by neutrophils and natural killer cells.[58] However, the exact mode of action of alemtuzumab and the exact function of CD52 are not fully understood.

The distribution of CD52 may account for the selective and beneficial mode of action of alemtuzumab and for the transient depletion of

both T- and B-lymphocytes. Importantly, because CD52 is found less frequently on innate immune cells, such as natural killer cells and phagocytes, alemtuzumab does not appear to disrupt other immune system functions. This could explain the relatively low rates of serious infections reported for alemtuzumab in clinical trials.

Pre-clinical mechanism of action studies on alemtuzumab have been limited by a lack of cross-reactivity between human and mouse CD52. However, significant insights into alemtuzumab's mechanism of action have been gained via studies in the recently developed transgenic mouse that expresses human CD52 (hCD52) under control of the hCD52 promoter.[58] The tissue distribution of hCD52 and immune function in the transgenic mice were normal. Treating the mice with alemtuzumab transiently increased serum cytokines and reduced blood lymphocytes in a manner that was similar to the response seen in humans. However, lymphocyte depletion was not as marked in lymphoid organs including the spleen, thymus and lymph nodes; this could explain why patients receiving alemtuzumab show a lower incidence of infection than might be anticipated. In mice, eliminating populations of natural killer cells and neutrophils with antibodies to Gr-1 or asialo-GM-1, respectively, markedly reduced the effects of alemtuzumab but removal of complement using cobra venom factor had no effect. These findings indicate that lymphocyte depletion resulting from alemtuzumab therapy relies primarily on antibody-dependent cell-mediated cytotoxicity as opposed to complement-dependent cytotoxicity. An overview of these potential mechanisms of action is shown in *Table 2*.

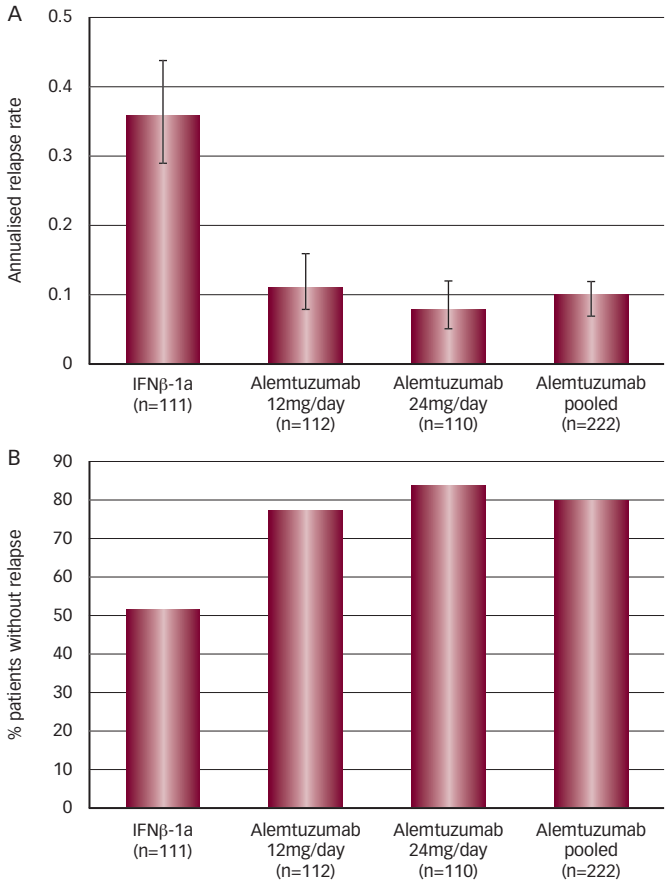
After alemtuzumab treatment, immune reconstitution follows a unique characteristic pattern in which B cells return towards baseline levels within three months while T cells take up to five years to recover.[59,60] Following peripheral lymphocyte depletion, it has been postulated that naïve myelin-specific T cells could be tolerised, preventing their neurodegenerative activity.[56] This property could provide alemtuzumab with immunomodulatory properties in addition to depleting lymphocytes.[59] Furthermore, *in vitro* analysis has shown that alemtuzumab may increase the lymphocytic delivery of neurotrophins to the central nervous system promoting survival of neurons and increased axonal length.[54] This potential neurorestorative action may partly explain the observed improvement in disability after alemtuzumab administration, although much work is required to further elucidate this effect. Overall, it appears that the benefits of alemtuzumab therapy in MS rest not on lymphocyte depletion per se, but rather in a long-term shift in the lymphocyte repertoire.

Alemtuzumab Clinical Trial Data

Initial pilot studies (1991–2002) consisting of 58 patients with MS showed that alemtuzumab significantly reduced relapse rates in both RRMS and secondary progressive MS (SPMS) (2.2–0.19 and 0.7–0.001 relapses per year, respectively, both p<0.001).[61] Moreover, in alemtuzumab-treated patients with either RRMS or SPMS there was no new lesion formation. It also produced sustained and significant reductions in disability progression in RRMS, but not in SPMS where disability accumulation was sustained.[61] Data from these pilot studies suggest that alemtuzumab may be more effective in treating MS in early active patients.

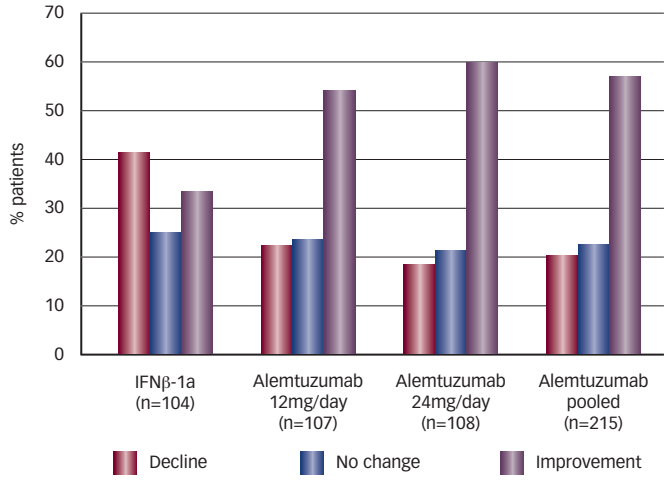
The phase II Campath-1H in Multiple Sclerosis (CAMMS223) trial provided the first well-designed controlled trial evidence in favour of alemtuzumab treatment in MS. This randomised study compared two doses of alemtuzumab with a current standard DMD treatment (IFNβ-1a SC) in a total of 334 DMD-naïve patients with early, active RRMS. Patients had an expanded disability status scale (EDSS) ≤3 and at least two clinical episodes during the previous two years.[62] Patients received intravenous alemtuzumab 12 (n=108) or 24mg per day (n=108, both doses were administered initially as a five-day course then a three-day course at 12 months and an optional 24 months) or IFNβ-1a 44µg SC three times weekly throughout the study (n=107). In CAMMS223, alemtuzumab showed markedly superior efficacy compared with IFNβ-1a in both the time to sustained accumulation of disability and the rate of relapse.[62] An analysis at 36 months demonstrated that the annualised relapse rates for patients receiving IFNβ-1a, or alemtuzumab 12 or 24mg per day and the pooled alemtuzumab analysis were 0.36, 0.11, 0.08 and 0.10, respectively (see *Figure 1*). Compared with IFNβ-1a, alemtuzumab both 12 and 24mg per day reduced the rate of relapse by 69 and 79%, respectively (p<0.001 for both comparisons). For six-month sustained accumulation of disability (SAD), greater improvements were observed for alemtuzumab-treated patients compared with those treated with IFNβ-1a. An estimated 26.2, 8.5, 9.5 and 9% of patients had SAD in the IFNβ-1a, the alemtuzumab 12 and 24mg per day groups and the pooled alemtuzumab analysis, respectively. Compared with IFNβ-1a, the alemtuzumab 12 and 24mg per day and pooled groups reduced the risk of sustained accumulation of disability (six-months' criteria) by 75,

Figure 1: Annualised Relapse Rates and the Percentage of Patients Without Relapse in the CAMMS223 Trial



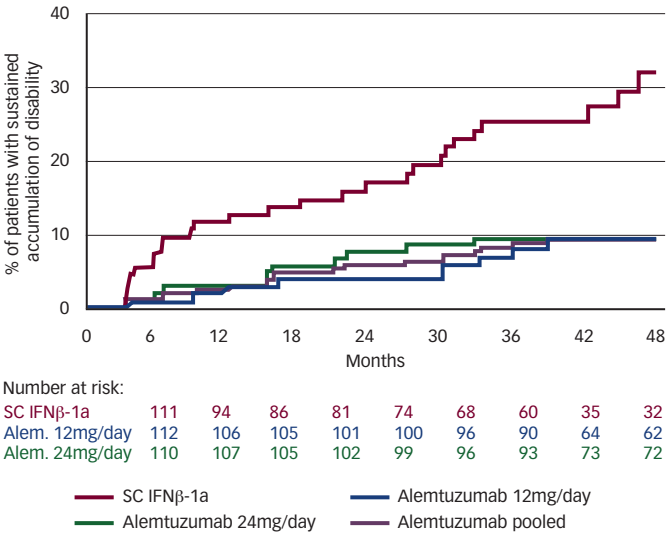
A: Annualised relapse rates; B: proportion of patients without relapses when receiving interferon beta-1a (IFNβ-1a) (44µg continuously, subcutaneous injection) or alemtuzumab (12 or 24mg per day, intravenous infusion) in the Campath-1H in Multiple Sclerosis (CAMMS223) trial (three-year data). *Alemtuzumab dosing regimen is initially for five days, then for three days after 12 months.*
Source: CAMMS223 Trial Investigators, 2008.[62]

Figure 2: Change in Disability Scores from the CAMMS223 Trial



Proportion of patients showing decline, no change or improvement in disability scores during treatment with interferon beta-1a (IFNβ-1a) (44µg continuously, subcutaneous injection) or alemtuzumab (12 or 24mg per day intravenous infusion) in the CAMMS223 trial (three-year data). *Alemtuzumab dosing regimen is for five days initially, then for three days after 12 months. Source: CAMMS223 Trial Investigators, 2008.*[62]

Figure 3: Kaplan–Meier Analysis of Sustained Accumulation of Disability in Patients on the CAMMS223 Trial



Kaplan–Meier analysis of sustained accumulation of disability in patients treated with interferon beta-1a (IFNβ-1a) subcutaneous (SC) or alemtuzumab (alem.) (pooled 12 or 24mg dose groups) during the Campath-1H in Multiple Sclerosis (CAMMS223) trial and follow-up. Source: Coles et al., 2010.[61]

67 and 71, respectively (p<0.001, p=0.003 and p<0.001). From baseline to 36 months, all treatment groups were observed to have a lower volume of lesions, as measured by T2-weighted MRI. In addition, significant reductions in lesion load from baseline were observed at 12 months (p=0.01) and 24 months (p=0.005) in patients receiving alemtuzumab compared with IFNβ-1a. The changes in mean EDSS score from baseline at 36 months were -0.32, -0.45 and -0.39 for alemtuzumab 12 and 24mg per day and the pooled alemtuzumab analysis, respectively (p=0.006, p<0.001 and p<0.001 for changes from baseline) but was +0.38 for IFNβ-1a (p<0.001 for comparisons between alemtuzumab and IFNβ-1a). This indicates an unprecedented improvement in disability status for patients receiving alemtuzumab but a deterioration for patients receiving IFNβ-1a. In addition, the proportion of patients observed to have improvements in disability scores was greater with alemtuzumab 12 and 24mg per day and pooled (54.2, 60.2 and 57.2%, respectively) than IFNβ-1a (33.7%) (see *Figure 2*).

The four-year follow-up of CAMMS223 patients show that the efficacy advantages of alemtuzumab compared with IFNβ-1a were sustained over long-term durations despite the fact that no further doses of alemtuzumab were given after two years and that the majority had not received a dose for three years.[63] In the pooled alemtuzumab groups, there was a 72% reduction in the risk of relapse and the proportion experiencing a relapse was approximately halved relative to the IFNβ-1a group. Annualised relapse rates were 0.1 for the pooled alemtuzumab groups and 0.34 for the IFNβ-1a group. With alemtuzumab there was a 73% reduction in the risk of SAD which is supported by the Kaplan–Meier analysis of SAD during the CAMMS223 study and through four-years of follow-up given in *Figure 3*. The percentage of patients with SAD was 9% for pooled alemtuzumab groups and 32% for the IFNβ-1a group. The significant improvement in disability for alemtuzumab was also maintained during four years of follow-up; the EDSS scores in the pooled alemtuzumab-treated patients improved by –0.43 (standard deviation [SD] = 1.04) whereas for IFNβ-1a the EDSS scores deteriorated by +0.25 (SD=0.96) (p<0.001). Therefore, the four-year data provide further evidence of the durability of benefit derived from alemtuzumab in producing clinically disease-free status and preventing clinical progression in a substantial majority of RRMS patients. This treatment effect is observed even in those patients who completed only two annual cycles of alemtuzumab during the first 12 months.[64]

Three-year data for the CAMMS223 trial show that the overall proportion of patients receiving alemtuzumab who reported AEs was greater than the proportion receiving IFNβ-1a. In the alemtuzumab groups, the most common AEs reported were infusion-associated reactions (98.6%). These reactions were confined to the alemtuzumab group due to the method of administration. These reactions included rash (91.7%), headache (61.1%), pyrexia (37.5%), fatigue (27.8%), pruritus (25.0%) and nausea (24.1%).

Notable AEs occurring in both the alemtuzumab (pooled analysis) and IFNβ-1a groups were: autoimmune thyroid disorders (23 and 3%), idiopathic thrombocytopenic purpura (ITP) (3 and 1%) and infections (66 and 47%).[62] Among the other events, the most frequent were influenza-like illness (4 versus 27%; p<0.001), fatigue (31 versus 30%), headache (31 versus 28%), pyrexia (11 versus 10%) and rash (26 versus 14%). Apart from influenza-like symptoms, the differences in incidence in these events between alemtuzumab- and IFNβ-1a-treated groups were not significant.[62]

The first case of ITP went unrecognised and following several weeks of typical symptoms, presented with a fatal cerebral haemorrhage. However, the other ITP cases were self-limiting or responsive to treatment, all patients achieved durable remission and no ITP was reported >16 months after treatment.[65] It was previously hypothesised that patients who had autoimmune AEs following alemtuzumab had a fundamentally different immune reconstitution and may be less likely to respond to treatment compared with patients without such events. The study data show that this is not the case; patients with autoimmune events through 36 months showed a 66% reduction in the risk of SAD (p=0.03) and a 78% reduction in risk of relapse

(p<0.0001) compared with patients receiving IFNβ-1a.[66] Therefore, patients who experienced autoimmunity were equally likely to benefit from alemtuzumab efficacy as those without such events.

In the CAMMS223 trial, one patient developed antiglomerular basement membrane (anti-GBM, Goodpastures syndrome). The patient developed hypothyroidism at month 24 (day 733) and at month 51 (39 month after the second alemtuzumab cycle), showed increased serum creatinine (1.9mg/dl at diagnosis and peaking at 2.8mg/dl) with haematuria. A renal biopsy showed anti-GBM. The patient also had an upper respiratory infection and rash, which are typical of anti-GBM, just prior to the onset of haematuria. The patient was treated with a course of plasmapheresis, cyclophosphamide and steroids. Seventeen months after diagnosis, the patient remains in remission with elevated but stable serum creatinine and is MS relapse-free. In CAMMS223 to date, only one patient has developed anti-GBM disease (frequency 0.5%, event rate one per 981 patient-years).[63,67]

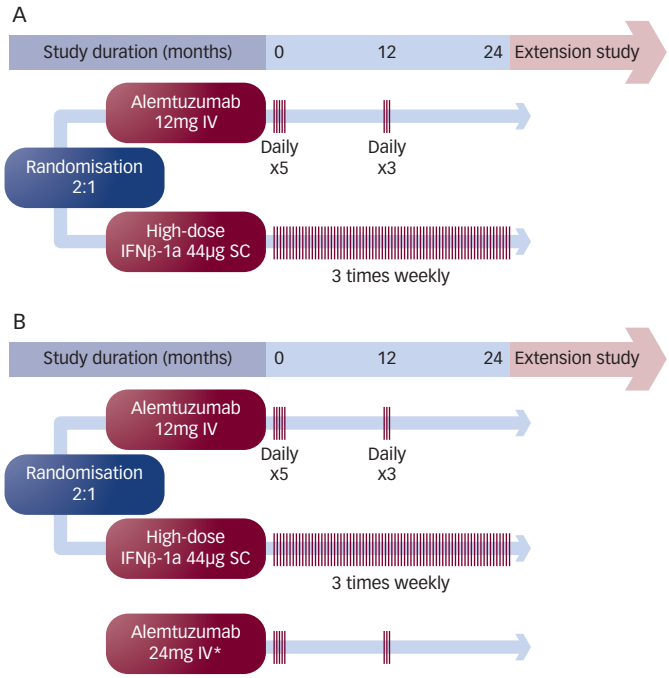
In MS patient populations treated with alemtuzumab to date, the incidence of any serious opportunistic infections has been low; and the infections that have occurred were mostly of mild to moderate severity.[62,65] However, the immunosuppressive effects of alemtuzumab may be selective with relative sparing of the lymphoid organs including the spleen, thymus and lymph nodes. These observations demonstrate a favourable safety profile but larger phase III trial safety data are awaited.

Hypotheses Concerning Delayed or Secondary Autoimmunity

The mechanism of action of alemtuzumab and the process by which it might induce secondary autoimmunity in a subset of MS patients have received attention in several studies. Recent clinical data on a subset of 94 of the 232 patients in the CAMMS223 trial who had RRMS and received alemtuzumab, has shown that those who develop lymphopenia-associated autoimmunity (mainly to the thyroid gland) have greater levels of T-cell apoptosis and T-cell cycling driven by substantially higher baseline levels (two-fold) of interleukin 21 (IL-21) than patients who do not develop autoimmunity.[68] The study also showed that IL-21 expression is genetically pre-determined. It was proposed that following lymphocyte depletion by alemtuzumab, overproduction of IL-21 in some individuals results in excess T-cell cycling and apoptosis and thereby increases the stochastic opportunities for T-cells to encounter self antigen, break tolerance and for autoimmunity to develop. Increased IL-21 levels may also act to promote B-cell differentiation and antibody production.[56] Therefore, IL-21 levels could be used as a biomarker prior to alemtuzumab treatment, to indicate which patients may be at increased risk of developing secondary autoimmunity.

Other immunological studies have shown that although lymphocytes are repeatedly depleted during cycles of alemtuzumab treatment, the capacity of the immune system to regenerate remains unimpaired. After exposure to alemtuzumab, B-cell reconstitution is rapid with levels returning to baseline by three months and to higher levels by 12 months.[60] The most abundant B cell subtype one month after treatment are immature transitional B cells. At the same time, there is an increase (33%) in serum levels of B-cell activating factor (BAFF) that is sustained for at least 12 months. BAFF is essential for transition of immature B cells to a mature naïve B-cell phenotype and it has been associated with the development of autoimmunity by an as yet, incompletely understood mechanism.[60] A potential factor contributing to autoimmunity following alemtuzumab treatment is the delayed proliferation of T-cell populations, including T-regulatory cells, at a time of rapid proliferation of unregulated B-cells.[54,60,69]

Figure 4: Study Design of CARE-MS I and CARE-MS II Phase III Clinical Trials



Study design of (A) Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis I study (CARE-MS I) and (B) Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis II study (CARE-MS II).
**Exploratory 24mg intravenous (IV) group with limited recruitment.*
IFNβ = interferon beta; SC = subcutaneous.

An Ongoing Clinical Development Programme for Alemtuzumab

The development programme of alemtuzumab consists of two large ongoing phase III trials with active comparators (i.e. no placebo arm) and an extension study. These will include both previously untreated patients and those who have relapsed on therapy. The first of the phase III trials is the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis I (CARE-MS-I) trial, which is a randomised, rater-blinded multicentre study comparing one dose level of alemtuzumab with IFNβ-1a in treatment-naïve patients with early active RRMS.[70] In this trial, a total of 581 patients have been randomised and alemtuzumab (12mg per day IV) was initially administered for five days and then for a three-day course at 12 months. The comparator (IFNβ-1a, 44µg SC) is to be given three times weekly throughout (randomised 2:1) (see *Figure 4*). The end-points include time to SAD, relapse rates, change from baseline in MRI-T2-detected hyperintense lesions, change from baseline EDSS and acquisition of disability as assessed by the multiple sclerosis functional composite (MSFC) over a two-year period.

The parallel study, CARE-MS II, includes patients with active RRMS who have relapsed at least once in the past 10 years while receiving either IFNβ or glatiramer acetate and have an EDSS score of 0.0–5.0.[71] A total of 840 patients have been enrolled in the trial. CARE-MS II includes two dose levels of alemtuzumab (12mg per day and an exploratory 24mg per day) and IFNβ-1a (44µg), (randomised 2:2:1)

(see *Figure 4*). The end-points are similar to CARE-MS I. Together, the results from these trials will further define the clinical profile of alemtuzumab in RRMS. An open-label extension study is also in progress for all patients from CAMMS223 and those completing CARE-MS I and II.[72] Alemtuzumab-treated patients will receive further alemtuzumab based on protocol-specified criteria of disease activity that include relapse or a minimum of two new lesions on cranial/spinal MRI consisting of any combination of gadolinium-enhancing lesions or new or enlarging T2 lesions. This treatment approach is innovative as it represents the first time where patients would receive MS therapy only on an as needed basis. IFNβ-1a-treated patients will receive annual courses of alemtuzumab (12mg per day for five days initially then for three days after 12 months) and then will have the option of further treatment based on the same criteria for the patients previously treated with alemtuzumab. The extension study is designed to assess the long-term efficacy and safety of alemtuzumab, define criteria for additional as needed alemtuzumab therapy and determine the safety and effectiveness of the alemtuzumab in patients who switch from IFNβ. As with the phase III studies, the extension study will include risk-monitoring programmes for autoimmune disease.

Implications of Study Data

The efficacy data from the phase II CAMMS223 trial provide strong evidence that alemtuzumab represents a major advance in the treatment of RRMS. Improvements over IFNβ-1a were seen in terms of reducing relapse rates, reducing both the number of lesions, the incidence of new lesions and decreasing progression of disability in patients with RRMS. Most surprisingly, the majority of patients treated with alemtuzumab in the CAMMS223 trial showed an improvement in disability scores compared with worsening scores with IFNβ-1a. This could indicate that for some patients in the early phase of the disease, treatment with alemtuzumab may reverse deficits by its potent immune modulating effect and allow physiologically effective repair in the central nervous system to occur. The potential finite treatment duration of alemtuzumab could fulfil a substantially unmet clinical need in MS and free patients from the necessity of constant DMD treatment. This administration regimen helps patients to forget about their diseases and achieves high levels of adherence resulting in durable remission. As the disease transitions into SPMS, the neuronal damage and axonal loss become more extensive, and with such high levels of damage, repair mechanisms appear unable to restore function. Alemtuzumab could potentially delay or prevent the onset of the secondary progressive phase.

Future Developments

In the future, there will be a greater choice of DMDs available to the neurologist for MS treatment. Choosing either of the current injectable agents, new oral agents or existing and new monoclonal antibody therapies will require an understanding of the therapeutic role of these medications and the development of guidelines. Immunomodulators have made great progress in the last few years, but it will be important for patients to be carefully monitored to ensure ongoing therapeutic effect. A patient must have a decreased number of relapses and reduced relapse severity compared with the pre-therapeutic phase, slowed disease progression and a lack of severe side effects that reduce QoL. The order in which MS treatments are used and methods for optimal dosing in individual patients will also need to be defined. As more clinical data become available, escalating immunotherapy options will need to be redefined.[33,73] The role of biomarkers in therapeutic monitoring and clinical outcomes is also likely to emerge in the near future, providing further guidance to the clinician.[7,74] The completion of the first decade of this century is heralding a new era of MS therapeutics. In this context, alemtuzumab offers great promise for MS patients. If the phase II data are replicated in the ongoing phase III trials, alemtuzumab may set the bar for therapeutic efficacy. If the long-term safety of this agent is acceptable and manageable, alemtuzumab may present itself as a potent and reasonable first choice in a long list of therapeutic options. ■

Omar A Khan is a Professor of Neurology and Director of the Multiple Sclerosis Clinical Research Center and Image Analysis Laboratory in the Department of Neurology at Wayne State University School of Medicine. His research and clinical interests include multiple sclerosis (MS) and related diseases, including neuromyelitis optica and transverse myelitis, high-risk MS pregnancy cases and neurological complications of lupus, sarcoidosis and vasculitis. Dr Khan also specialises in the treatment of aggressive forms of MS with chemotherapy and other emerging treatments.

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