

# Expert Opinion

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## Alemtuzumab and multiple sclerosis: therapeutic application

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**Importance of the field:** The cause and cure for multiple sclerosis (MS) remain unknown. Immunomodulatory agents are only partially effective and many patients do not tolerate the side effects or fail them. Immunosuppressive agents act non-specifically and are associated with serious complications. An emerging group of biologic agents with great potential for treatment of immune-mediated disorders such as MS are monoclonal antibodies. A review of alemtuzumab in MS is presented.

**Areas covered in this review:** Mechanisms of action of alemtuzumab and the results of Phase II clinical trials in MS.

**What the reader will gain:** Alemtuzumab is a humanized mAb, which targets the surface molecule CD52 on all T cell populations and other cellular components of the immune system such as thymocytes, B cells, and monocytes. Alemtuzumab, which is administered intravenously, depletes T as well as B lymphocyte populations for extended periods. Adverse effects in MS patients such as thyroid disorders and idiopathic thrombocytopenic purpura are discussed.

**Take home message:** Alemtuzumab may hold great promise for treatment of MS patients and serve as an option for patients refractory to immunomodulatory therapies. Due to its unique mechanism of action and profound effect on MS disease activity it enhances our knowledge about pathogenic mechanisms of MS.

**Keywords:** alemtuzumab, Campath, CD52, monoclonal antibody, MRI, multiple sclerosis

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### 1. Introduction

Therapeutic strategies for patients with multiple sclerosis (MS) have evolved from non-specific immunomodulation and immunosuppression to the development of highly selective monoclonal antibodies, which target selective molecules or antigens in the immune system with highly specific results. While for the past two decades monoclonal antibodies have been utilized by the oncologists to treat various cancers, this group of therapeutic agents is relatively new to the neurologists and only recently their potential and very selective anti-inflammatory properties for treatment of neuro-inflammatory disorders have been discovered. Natalizumab (Tysabri), an anti-VLA-4 monoclonal antibody, has been approved by the FDA for treatment of patients with relapsing-remitting MS (RRMS). Three other monoclonal antibodies – daclizumab, rituximab, and alemtuzumab (Box 1) – are currently under clinical development for treatment of patients with MS. Each one of these monoclonal antibodies has a highly selective and different mechanism of action and targets a particular antigen expressed by the immune cells. Apart from these monoclonal antibodies, currently a novel group of oral immunosuppressive agents for treatment of MS are under clinical investigation. These agents include fingolimod, Cladribine and BG-12. We present a detailed review of mechanism

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**Box 1. Drug summary.**

Drug name	Alemtuzumab
Phase	III
Indications	Multiple sclerosis
Pharmacology description	Lymphocyte inhibitor CD52 antagonist Immunosuppressant
Route of administration	Parenteral, intravenous
Pivotal trial(s)	[49-55]
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of action of alemtuzumab and describe the results of clinical trials of alemtuzumab in MS patients.

## 2. Multiple sclerosis: a brief review of pathogenesis

Multiple sclerosis (MS) is the most common cause of neurological disability in young adults and runs a progressive and unpredictable course. The etiology and cure of MS remain elusive and its relapsing and often relentlessly progressive nature poses significant economic and mental pressure on the patient, their family members, and society. Like other immune-mediated disorders, the etiology of MS has been subject to speculations. Based on prevailing hypotheses, pathogenesis of MS involves the interactions among environmental factors, genetic background and immune system, which ultimately evolves into inflammatory demyelination, axonal loss and neurodegeneration. Abnormal activation of both the cellular and humoral arms of the immune system against CNS antigen(s) [such as members of myelin basic protein family, MBP myelin oligodendrocyte glycoprotein, galactocerebroside and contactin-2] is associated with disruption of the blood-brain barrier (BBB), egress of the MBP-autoreactive leukocytes and other mediators of inflammation such as cytokines and chemokines through the cerebral endothelial cells leads to widespread inflammatory as well as neurodegenerative responses within the CNS milieu [1-3]. Transendothelial migration of activated leukocytes from periphery to brain and spinal cord is a prominent feature of pathogenesis of MS, which occurs following the expression of adhesion molecules, such as members of the selectin and integrin family, on the surface of postcapillary venules. Once the activated leukocytes bind to the underlying activated endothelium, they release matrix metalloproteinases which facilitates digestion of the fibrin and basement membrane collagen as well as cerebral endothelial cells' junctional proteins such as occluding and VE-cadherin to establish a pathway for migration of these cells [4,5]. Once the activated leukocytes gain access to the CNS environment they continue the destructive inflammatory demyelination through multiple mechanisms which include various cytokines, chemokines,

antibody- and complement-dependent reactions, free radicals and excitatory amino acids. According to the autoimmunity hypothesis for pathogenesis of MS, activated T lymphocytes within the CNS environment differentiate into  $T_{H1}$ ,  $T_{H2}$ ,  $T_{H3}$ , or  $T_{H17}$  cells [6,7].

$T_{H1}$  lymphocytes, which express high levels of activation molecules (HLS-DR and CD71) along with co-stimulatory molecules (CD80/B7-1), are associated with autoimmune diseases [8]. These cells preferentially release pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$  and IL-12, which are associated with relapses of MS [9-11]. The  $T_{H1}$  cytokines promote the inflammatory cascade in MS and induce damage [12]. On the other hand,  $T_{H2}$  lymphocytes synthesize and release the anti-inflammatory or protective cytokines such as IL-4, IL-5, IL-6, IL-10 and IL13. Other subsets of T lymphocytes which are involved in ameliorating of the inflammatory cascade of MS include CD4 regulatory cells such as FOXP3<sup>+</sup>CD4<sup>+</sup>CD25<sup>high</sup> regulatory T cells, the IL-10-generating Tr1 cells, and the  $T_{H3}$  regulatory cells which produce transforming growth factor- $\beta$  [6,13].

A newly identified subset of CD4<sup>+</sup> T lymphocytes, termed  $T_{H17}$  cells express IL-17, IL-6 and TNF- $\alpha$  [14,15]. Based on a number of scientific observations expression of IL-17 and another related cytokine, IL-23, are elevated in CNS lesions and in peripheral blood mononuclear cells of patients with MS [14,16-19]. In addition, experiments on IL-17-deficient mice have demonstrated a significant reduction of disease severity in these knockout animals. The evidence obtained from MS lesions and animals with experimental autoimmune encephalomyelitis (EAE) promote the concept of IL-17 as a significant promoter of autoimmunity in pathogenesis of MS [20].

Recently, the role of humoral arm of the immune system and activity of B cells in the pathogenesis of MS has been scrutinized. Under normal circumstances, B lymphocytes do not egress the BBB; however, during the massive immune activation which occurs in pathogenesis of MS, an antigen-driven influx of these lymphocytes to the CNS occurs, which results in persistent generation of oligoclonal immunoglobulin in the cerebrospinal fluid, continuous intrathecal synthesis of immunoglobulins, B lymphocyte clonal expansion and somatic hypermutation [21,22] and formation of secondary lymphoid tissue in brains of patients with secondary progressive MS [23].

## 3. Biology of CD52

The human CD52 gene is located on chromosome 1 and two alleles are recognized [24]. The CD52 antigen consists of a glycosylphosphatidylinositol (GPI) anchored glycoprotein of 12 amino acids and is expressed with high density of approximately  $5 \times 10^5$ /cell on B and T lymphocytes. As an antigen, CD52 is expressed during the leukocyte differentiation process and is displayed on cellular membrane. In humans, CD52 is significantly expressed by both normal and malignant

peripheral T and B lymphocytes and to a lesser extent by monocytes, eosinophils, and macrophages [25-27]. CD52 has minor expression by mature NK cells and hematological stem cells [28,29]. In addition, the CD52 antigen is generated by other cells such as the epithelial cells in the epididymis and duct deferens and is acquired by spermatozoa once they travel through the genital tract [30]. CD52 antigen presents as an accessible target for alemtuzumab. In addition, CD52 is expressed at low concentrations at the surface of CD34<sup>+</sup> hematopoietic cells, parent stem cells for CD52<sup>+</sup> lymphocytes [31,32], therefore, use of alemtuzumab is associated with annihilation of mature lymphocytes without myeloablation. While the exact biological function of CD52 remains unknown, some evidence suggests that it is involved in T lymphocyte migration and costimulation [33-36]. The C-terminal portion of the protein and a part of the GPI are identified by alemtuzumab, which in turn advances complement deposition and formation of the membrane attack complex for induction of cell lysis [complement dependent cytotoxicity/cytolysis] [37]. Alternatively, alemtuzumab is believed to promote antibody-mediated cellular cytolysis because of its IgG Fc region [38]. Another mechanism of action for lymphocyte depletion by alemtuzumab is lymphocyte apoptosis *in vitro* in the absence of complement or other immune effector cells. Based on this mechanism lymphocyte apoptosis occurs via a non-classical caspase-independent pathway (Figure 1) [39]. Lastly, alemtuzumab may activate caspase-dependent apoptotic mechanisms in order to deplete lymphocytes [40]. Apart from the remarkable suppressive effects of alemtuzumab in MS, the fate of B lymphocytes following treatment of these patients with alemtuzumab is interesting. Thompson *et al.* [41] investigated the effect of alemtuzumab on B lymphocytes and demonstrated that B lymphocyte reconstitution is fast and these cells return to baseline by 3 months and rise to 165% of baseline by 1 year after therapy. Based on the results of this study, the depleted B-cell pool was dominated by recent bone marrow emigrants (cells with a T1 phenotype [CD19<sup>+</sup>/CD23<sup>-</sup>/CD27<sup>-</sup>]). However, by month three following treatment with alemtuzumab, mature naïve B lymphocytes (cells with CD19 and CD23 positive staining but CD27 negative) dominated the pool of B lymphocytes. These events coincides with a surge in serum B-cell activating factor (BAFF), which remains elevated by 33% for at least 12 months following treatment with alemtuzumab. The authors concluded that in these patients, differentiation to memory B lymphocytes was slow and B lymphocyte pool after treatment with alemtuzumab showed fundamental and protracted alterations.

The concept of the utilization of a humanized monoclonal antibody against CD52 antigen in MS originates from earlier uncontrolled pilot trials suggesting that pulse therapy with alemtuzumab, as a monoclonal antibody which targets T and B lymphocytes, increased the long-term allograft acceptance in animals [21,42-46]. In addition, it was previously demonstrated that sustained lymphocyte depletion in MS

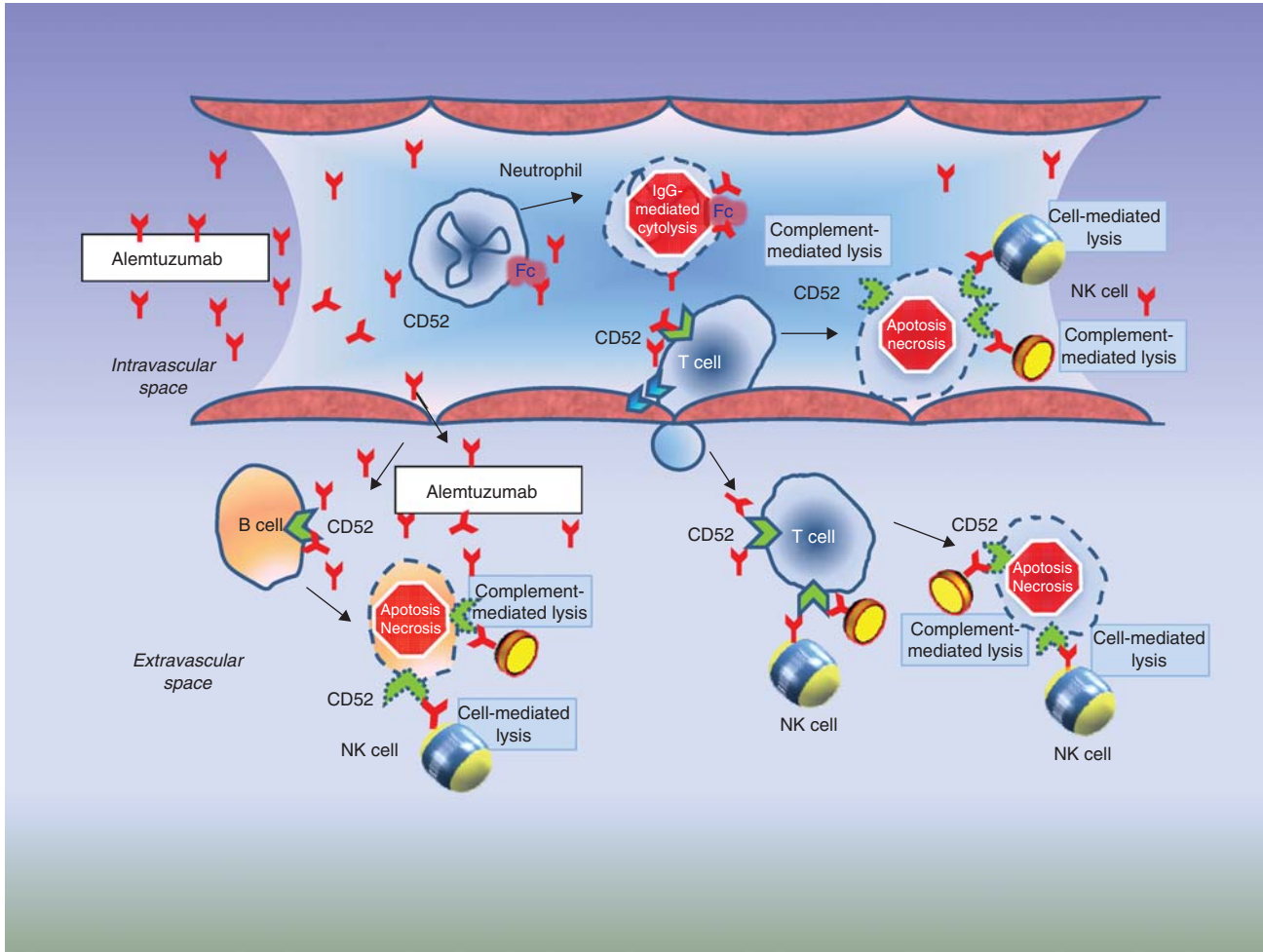
patients was associated with suppressed disease activity as evidenced by reduction in new lesion formation on brain MRI [47].

#### 4. Clinical trials of alemtuzumab in multiple sclerosis

Alemtuzumab (Campath-1H) is a genetically engineered humanized IgG1κ mAb, which recognizes and binds to the CD52 antigen expressed at the surface of thymocytes, NK cells, B lymphocytes and T lymphocyte populations [29-37]. Alemtuzumab is a Y-shaped molecule which consists of two 24 kDa light polypeptide chains and two 55 kDa heavy polypeptide chains. The light and heavy chains are linked by two intersulfide bridges between light and heavy chains and two intersulfide bridges between heavy and heavy chains. Furthermore, the alemtuzumab molecule possesses 12 inter-chain disulfide bridges and an asparagine residue in each heavy chain which is amenable to glycosylation [48]. The genetically altered molecular structure of alemtuzumab is composed of six different complementarily-determining regions (CDRs) which are derived from IgG2a rat monoclonal antibody. These rat-derived CDRs are specific for the 21 – 28 kDa lymphocyte cell surface glycoprotein, CD52. Currently, alemtuzumab is approved by the FDA for treatment of B-cell chronic lymphocytic leukemia (B-CLL). The exact function of CD52 in the immune system remains unknown.

For decades, MS has been identified and researched as a T lymphocyte-mediated disease, therefore, the concept of use of alemtuzumab as a potential treatment to deplete lymphocyte populations in order to slow down disease activity and to delay the onset of disability in MS appears attractive and reasonable. Alemtuzumab was initially used to treat patients with secondary progressive MS [49]; however, despite effective immunosuppression MS patients in the progressive phase of disease continued to accrue disability. Based on this observation, it was conjectured that alemtuzumab would be more effective in those patients with a strong inflammatory component who have not entered the ‘neurodegenerative phase’ of MS – mainly patients with relapsing–remitting MS. Promising results obtained from preliminary clinical trials of alemtuzumab in MS in the UK and USA led to devising and execution of larger clinical trials of this mAb in MS.

One of the first clinical trials utilizing alemtuzumab, as an anti-leukocyte mAb, for treatment of MS was conducted by Coles and colleagues [49]. During this open-label clinical trial, a cohort of 27 patients with secondary progressive MS underwent a single course of treatment with alemtuzumab. The subjects were then followed up clinically and by brain MRI for 18 months post treatment. In addition, the patients were randomized to treatment with an infusion of either methylprednisolone, a soluble TNF-α receptor, or no additional therapy prior to first infusion of alemtuzumab. While disease activity continued for a number of weeks following the treatment with alemtuzumab, later on clinical relapses and



**Figure 1. Molecules of alemtuzumab target CD52 antigen present on the surface of T and B cell lymphocytes, neutrophils and natural killer cells.** Alemtuzumab causes cell lysis via two different mechanisms: antibody-mediated cellular cytotoxicity and complement-dependent cytotoxicity.

cerebral inflammation were significantly suppressed for at least 18 months, as documented by a prominent decrease in the number of T1-weighted post-contrast enhancing lesions on brain MRI [50]. No increase in T2 lesion volume (LV) occurred between 6 and 12 and 12 and 18 months of treatment. Treatment of the study subjects with alemtuzumab did not have any significant effect on the progression of brain atrophy [50]. Reduction in brain volume was related to the change in T1 hypointense LV after treatment. A reduction in spinal cord area was also seen throughout the study duration, and this correlated with an increase in disability [50].

In a one-year prospective clinical trial involving 16 MS patients, Cox *et al.* [51] assessed lymphocyte homeostasis following therapeutic lymphocyte depletion with alemtuzumab. Study subjects were treated with a single therapeutic course of alemtuzumab. The investigators noted two stages of lymphocyte reconstitution: during the first six months following the pulse therapy the precursor frequency and

proliferation index of patients' autologous mixed lymphocyte reaction were elevated and memory T lymphocytes ( $CD4^+CD45RO^+$ ) dominated the lymphocytic profile. In addition, prior to treatment with alemtuzumab there was no difference between study subjects and healthy controls in the proportion of  $CD4^+$  T lymphocytes that expressed  $CD4^+CD25^{high}$ . However, after treatment with alemtuzumab the  $CD4^+CD25^{high}$  regulatory T lymphocytes were over-represented in the depleted  $CD4^+$  pool. During this period, non-significant elevation of the peripheral mononuclear cell FoxP3 mRNA expression and decrease in constitutive cytokine mRNA expression was detected. During the second half of the study (months 6 – 12) these alterations were returned to the levels observed prior to treatment with alemtuzumab and the expression of repressor of GATA-3 mRNA was increased. Despite these reversals, the total  $CD4^+$  lymphocyte counts remained less than 50% of pre-treatment levels at 12 months. This was attributed to

defective homeostasis, which was not due to an impaired IL-7 response, as is observed in rheumatoid arthritis nor to lack of IL-7 receptors. The investigators suggested that the failure of homeostasis in MS patients was due to suboptimal CCL21 and IL-15 responses.

In another clinical trial, Hirst *et al.* [52] reported the results of an open label trial of alemtuzumab in a cohort of 39 highly selected patients with aggressive MS who were treated across three regional centers. The patients were first treated with methylprednisolone (1000 mg/daily for three days). Then four different treatment regimens were used; two subjects were treated with alemtuzumab at 30 mg daily for five days, 11 subjects were treated with alemtuzumab at 24 mg daily for 5 days, 12 subjects received 20 mg daily for 5 days, and 13 subjects were treated with 12 mg daily for five days. The subjects were followed for a mean of 1.89 years. Based on the results of this trial, the mean annualized relapse rate decreased from 2.48 prior to therapy to 0.19 after therapy with 29% of documented relapses occurred in the 12 weeks following the initial infusion. Utilization of alemtuzumab was associated with mean change in Expanded Disability Status Scale (EDSS) of -0.36 overall and -0.15 in those who completed the study for more than one year of follow up. The disability status remained stable or improved in 83% percent of study subjects. Adverse events associated with infusion of alemtuzumab in this study included rash, headache and pyrexia. In three subjects, temporary worsening of pre-existing neurological abnormalities was noted. In 12 subjects, biochemical evidence of autoimmune dysfunction was detected, 2 subjects developed thyroid problems and 1 subject developed autoimmune skin disease. The investigators concluded that while administration of alemtuzumab to MS patients resulted in a decrease in relapse rate, certain adverse events were likely to develop. These adverse events were self-limiting or easily treated.

Coles *et al.* [53] in a Phase II clinical trial compared the efficacy of alemtuzumab versus IFN- $\beta$ 1a (Rebif) in subjects with early relapsing-remitting (RR) MS. The investigators assigned 334 MS patients with EDSS values of 3.0 or less and a disease duration of < 3 years to receive either IFN- $\beta$ 1a (44  $\mu$ g subcutaneously three times weekly) or annual intravenous infusion cycles of alemtuzumab at two different doses (12 mg or 24 mg daily) for 36 months. Each group that received alemtuzumab (12 mg or 24 mg) was treated with intravenous infusion of alemtuzumab on five consecutive days during the first month and on three consecutive days at months 12 and 24. The results of this clinical trial demonstrated that treatment of MS subjects with alemtuzumab was associated with a significant 71% reduction in the rate of sustained accumulation of disability and reduction of the rate of relapse by 74% as compared with IFN- $\beta$ 1a. Moreover, mean disability score, as measured by the EDSS, improved by 0.39 points in alemtuzumab patients but worsened by 0.38 points in the IFN- $\beta$ 1a patients ( $p < 0.001$ ). From the initiation of the study to 36 months, in all the three study groups, a reduction in the T2-LV was detected; however, this reduction was more

noticeable in the subjects treated with alemtuzumab than in those treated with IFN- $\beta$ 1a ( $p = 0.005$ ). In addition, from month 12 to month 36, whole brain volume, as measured by the Losseff method on T1-weighted sequences [54] increased in those who were treated with alemtuzumab but decreased in the IFN- $\beta$ 1a-treated subjects. The investigators reported that there were no significant differences in trial outcomes between the 12 mg dose and 24 mg dose of alemtuzumab. The reported adverse events associated with treatment of MS patients with alemtuzumab consisted of infections, thyroid disorders and idiopathic thrombocytopenic purpura (ITP). A case of anti-glomerular basement membrane disease in a 40-year-old white female with relapsing-remitting MS has been reported. The patient was treated with a total dose of 100 mg of alemtuzumab [55].

Two large Phase III studies were designed to confirm and extend the results of Phase II trial. Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS I) is a randomized, rater-blinded study comparing the safety and efficacy of alemtuzumab to subcutaneous IFN- $\beta$ 1a (Rebif) in treatment naïve patients with RRMS. Eligible candidates are patients with RRMS who experienced at least two MS relapses within 24 months, including one relapse more within 12 months prior to study entry. CARE-MS II is a randomized, rater-blinded study comparing the safety and efficacy of alemtuzumab to subcutaneous IFN- $\beta$ 1a in patients with active RRMS who have experienced two relapses in the last two years, including one relapse in the last 12 months prior to study entry during prior treatment with IFN- $\beta$  or glatiramer acetate, after having received that therapy for at least 6 months. Both of these studies are currently closed to new enrollment and the results are anticipated in the next two years.

## 5. Adverse effects and complications of alemtuzumab

Despite its ease of administration and its superior efficacy, a number of potentially dangerous adverse events and complications may occur months to years following alemtuzumab utilization. Shortly following infusion of alemtuzumab, patients may experience fever, rash, headache, nausea and vomiting, and rigor, which are attributed to cytokine release. In addition, an early exacerbation of pre-existing deficits which may last a few hours and may be related to sudden increase in release of TNF- $\alpha$ , IFN- $\gamma$  or IL-6 [52,56]. In addition, a decline in CH50 suggesting complement activation following administration of alemtuzumab has been reported [56]. It has been demonstrated that pre-treatment of MS patients with corticosteroids, acetaminophen, or diphenhydramines may lessen such an inflammatory response [49,52,56]. While pulsed therapy of patients with early RRMS with alemtuzumab is significantly effective in suppression of disease activity, up to 30% of MS patients may develop autoimmune thyroid disorders, predominantly Graves' disease and more uncommonly autoimmunity against blood components [53,57]. Interestingly, cancer patients

treated with alemtuzumab do not develop autoimmune thyroiditis and this complication has only been reported in patients with immune-mediated diseases such as MS and anti-neutrophil cytoplasm antibody-associated vasculitis patients receiving alemtuzumab [58]. This significant observation emphasizes the role of the immune system in development of autoimmune thyroiditis in the MS population. Recently, Jones *et al.* [57] demonstrated that increased lymphocyte proliferation and apoptosis are generic responses to alemtuzumab treatment, however, secondary autoimmunity occurred in treated MS patients exhibiting the greatest level of T cell apoptosis. Given there were no differences in the rates of T cell reconstitution between the two groups, they inferred that increased T cell cycling occurred in the autoimmune group, presumably driven by higher serum levels of IL-21. In fact, prior to treatment with alemtuzumab, patients with more than two-fold greater serum levels of IL-21 developed secondary autoimmunity compared with those patients who did not develop such complications. The authors propose that IL-21 is an indicator for the potential of developing secondary autoimmunity following therapy with alemtuzumab. They also suggest that IL-21 pushes the cycles of T cell expansion and apoptosis to higher levels, which in turn increases the stochastic chances for T cells to encounter self antigen and formation of autoimmune responses. Idiopathic thrombocytopenia (ITP) was the other complication that was observed among MS patients who were treated with alemtuzumab. There has been an almost 3% risk of developing ITP among MS patients. During the clinical trial of alemtuzumab for MS, one of the patients who developed ITP died due to fatal cerebral hemorrhage [59]. Subsequently, while treatment of MS patients with alemtuzumab was suspended, the clinical trial of alemtuzumab was continued and an amendment and a risk management plan, which mandated more frequent complete blood count measurements and education and monthly site contact with the patient was implemented. In addition, development of renal failure due to Goodpasture's disease associated with utilization of alemtuzumab in MS has been reported [60].

The clinical trial of alemtuzumab versus IFN- $\beta$ 1a revealed only mild-to-moderate infections, particularly of the respiratory tract, being more frequent among those who received alemtuzumab than those receiving IFN- $\beta$ 1a [53].

In terms of malignancy following treatment with alemtuzumab, three cases of cancers (non-EBV-associated Burkitt's lymphoma, breast cancer and cervical cancer *in situ*) [53] and one case of melanoma [61] have been reported.

## 6. Conclusion

Similar to other mAbs that are currently under clinical investigation for treatment of MS, alemtuzumab appears promising. The concept of depletion induction of immunosuppression is quite appealing and practical. A massive ablation of the lymphocytes will have a profound effect on the inflammatory cascade of MS and for the most part

suppresses the adaptive immune system and new lesions formation. However, while Coles *et al.* [53] in their 3-year-long clinical trial reported a statistically significant effect on sustained disability, it remains to be determined whether or not such profound and long lasting lymphopenia will slow down mechanisms of disease progression and delay the onset of disability in these patients beyond this and whether treatment with alemtuzumab will have any effect on the neurodegenerative process of MS, which most probably occurs independently from neuroinflammation. It is well known that neurodegenerative process in MS which is associated with loss of myelin and axons may be independent of the neuroinflammatory component of MS. Therefore, immunosuppression may not have any significant effect on this component of MS pathogenesis [62]. On the other hand, one can argue that ongoing neuroinflammation may trigger or promote neurodegeneration in MS patients. Treatment of patients with secondary progressive MS with alemtuzumab was associated with a significant reduction in number of relapses as well as T1-weighted contrast enhancing lesions, which indicates successful immunosuppression. However, disease progression was not discontinued [49]. Currently, due to the short duration of all clinical trials of alemtuzumab in MS patients, a reasonable response can not be proposed. Long term follow up of the MS patients who have been treated with alemtuzumab is required to resolve this fundamental question.

Another significant lesson learned from alemtuzumab trials is that the concept of one course of treatment every year most probably addresses the issue of compliance and will be very attractive for many MS patients who are not comfortable with frequent injections or who fail current treatments despite being compliant. However, like many other innovative treatments for incurable diseases such as MS, the long-term effects and complications of this mAb remain unknown. MS is a chronic disease with a clinical course that spans several decades. We do not know what will happen to our MS patients a decade after initiating treatment with alemtuzumab or other mAbs. Whether these patients will succumb to unusual and uncommon malignancies or will be subjected to other immune-mediated disorders such as ITP remain to be defined.

## 7. Expert opinion

Currently, alemtuzumab is under meticulous clinical investigation for treatment of MS patients. While alemtuzumab works through immunosuppression, depleting both B and T cells makes it more effective compared with other mAbs utilized for treatment of MS. In addition, while its one course per year treatment potentially improves the issue of treatment compliance, the main advantage of alemtuzumab over other agents rests on its superior efficacy and the remarkable reduction in disability observed following its use. From a socioeconomic viewpoint, alemtuzumab will probably be marked as an expensive option for treatment of MS and only in selected cases, based on proper documentation of

failure of other less expensive immunomodulatory agents. Due to its serious and potentially deadly adverse events, application of alemtuzumab may best be kept as the second line of treatment for patients with severe and frequent relapses. Probably it should not be offered to newly diagnosed treatment-naïve MS patients as the first choice of treatment. In addition, since patients who are treated with alemtuzumab must be monitored periodically for opportunistic infections as well as ITP, follow up of chronically immunosuppressed non-compliant patients will be a significant problem for the treating neurologist. Most probably this novel mAb will be used with great caution by treating physicians due to the risk of ITP and Graves' disease. Further safety data, which can be collected over the course of several years, particularly about development of opportunistic infections and uncommon malignancies, are required to make a more meaningful decision about using alemtuzumab. The anticipated FDA approval of other oral agents for treatment of MS such as

cladribine and fingolimod and their imminent introduction to the market may reduce the use of alemtuzumab significantly.

### Declaration of interest

A Minagar is the principal investigator for alemtuzumab trial in MS at LSUHSC-Shreveport. R Zivadinov has received personal compensation from Teva Neuroscience, Biogen Idec, EMD Serono and Questcor for speaking and consultant fees in the last 12 months. He has also received financial support for research activities from National Institute of Health, National Multiple Sclerosis Society, National Science Foundation, Biogen Idec, Teva Neuroscience, Genzyme, Bracco, Questcor, EMD Serono and Aspreva in the last 12 months. He is the Principal investigator for MRI re-analysis of the CAMMS223 trial and for the MRI analysis of the extension phase of the same study. The other authors declare no conflicts of interest.

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