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ORIGINAL COMMUNICATION

Efficacy and safety of alemtuzumab in a real-life cohort of patients with multiple sclerosis

Jessica Frau[1] · Giancarlo Coghe[1] · Lorena Lorefice[1] · Giuseppe Fenu[1] · Luigina Musu[1] · Eleonora Cocco[1]

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Abstract

Background No postmarketing randomised clinical trials are available about alemtuzumab, and real-world data are limited. We aimed to analyse the efficacy and safety of alemtuzumab in a single-centre cohort of patients with relapsing–remitting MS.

Methods Patients who took alemtuzumab were enrolled. We collected the following data: age, sex, MS history, expanded disability status scale (EDSS), relapses, magnetic resonance imaging (MRI) parameters after alemtuzumab, and adverse events. EDSS scores before alemtuzumab and at the last follow-up were compared by Wilcoxon test. Time to first relapse was analysed after dividing the cohort on the basis of previous treatment.

Results Ninety patients were enrolled [women 74.4%; naïve 7; mean follow-up 27 months (SD 23)]. The EDSS was reduced from a median of 2.5 (IQR 1.5–4) before alemtuzumab to 2.0 (IQR 1.5–3.5) after ($p=0.025$). The time to first relapse was shorter in patients shifting from a second-line therapy ($p=0.011$). Over 2 years, 43.7% had no evidence of disease activity. We observed infusion-related reactions in 95.5% patients, including 11.1% with pneumonitis, thyroiditis in 11%, and thrombocytopenia in 3.3%.

Conclusions We confirmed the clinical and MRI efficacy of alemtuzumab in the clinical setting and the frequency of infusion-related reactions. Compared with that in clinical trials, higher number of patients developed pneumonitis during infusion.

Keywords Alemtuzumab · Real-life · Efficacy · Safety

Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system. Both T and B lymphocytes are involved in the pathogenesis of MS [1]. The treatment approach for patients with MS has evolved over time. In particular, an increasing number of disease-modifying drugs (DMDs) have been tested and approved for patients with a relapsing remitting (RR) course, although only one of these drugs is also available for patients with progressive MS [1, 2].

Alemtuzumab is an anti-CD52 monoclonal antibody; the efficacy of alemtuzumab in the reduction of relapse rate and long-term disability and in magnetic resonance imaging (MRI) outcomes has been widely demonstrated in one phase II (CAMMS223) and two phase III clinical trials (CARE-MS I and CARE-MS II) [3–5]. Moreover, the efficacy of alemtuzumab has been confirmed by extension studies over a follow-up of 5 years [5–7]. Clinical trials have also provided data regarding the safety profile of the drug, showing a high frequency of infusion-related reactions (about 90% of exposed patients); an increased incidence of upper respiratory tract, urinary tract, and herpes infections; and a higher risk of acquired autoimmune diseases [8]. Unfortunately, as is the case for most available DMDs, no randomised clinical trials have been conducted in the postmarketing stages [9], and data derived from real-world situations are limited [10]. Notably, many individual cases have been described from various authors regarding unexpected adverse events (AEs) and abnormal reactivation of the disease after alemtuzumab treatment [11–17]. However, few cohorts have been analysed, and some have focused on evaluating particular conditions, in which patients have been shifted from fingolimod to alemtuzumab [18–21].

Therefore, in this study, we aimed to present data regarding efficacy and safety of alemtuzumab in a single-centre cohort from Italy, where this drug was originally approved

✉ Jessica Frau
jessicafrau@hotmail.it

[1] Multiple Sclerosis Center, University of Cagliari/ATS Sardegna, Via Is Guadazzonis, 2, 09126 Cagliari, Italy

by the Italian Medicines Agency (AIFA) in 2015 for naïve RR patients with early highly aggressive MS and for patients who did not respond to a first-line therapy.

Methods

Patients enrolled in this study were affected with RRMS, referred to the Regional Sardinian Centre for the Diagnosis and Treatment of MS (University of Cagliari/ATS Sardegna), and started on alemtuzumab treatment from 2009 until 2018 due to the aggressive disease course or high risk of progressive multifocal leukoencephalopathy (PML) during natalizumab treatment, according to inclusion criteria of the CAMMS 324 clinical trial and AIFA indications. We considered as having high PML risk during natalizumab both the patients with triple positivity (JCV antibodies, previous immunosuppressant DMDs, and more than 24 infusions), and those who underwent more than 24 infusions and JCV index > 1.5 (Stratify II). All patients enrolled in this study provided informed consent before initiation of therapy, agreeing to the use of their data for research purposes by healthcare professionals. Additionally, the local ethics committee approved this study.

Demographic, clinical, and radiological data were prospectively collected from medical records by neurologists with high expertise in MS. The same staff reported the data in an electronic database, which is periodically updated. The following features were recorded: age, sex, year of MS onset, previous DMD and reason for withdrawal, date of alemtuzumab courses, expanded disability status scale (EDSS) before alemtuzumab and annually after the first course, date of relapse after alemtuzumab, date of all MRI scans performed after alemtuzumab and the presence of new T2 or gadolinium (Gd)-enhanced lesions, alemtuzumab drop-outs, DMD after alemtuzumab, and AEs related to alemtuzumab. The evaluation of "no evidence of disease activity" (NEDA) was performed in our study over 2 years from the start of alemtuzumab treatment for the subgroup of patients with at least 2 years of follow-up and complete data for MRIs, relapses, and EDSS scores (NEDA-3). The NEDA is a measure of the disease activity-free status used in clinical trials on MS and has also been proposed in clinical practice. It is defined as the absence of relapses, disability progression, and MRI activity over a defined period of time [22]. A third and fourth course of alemtuzumab was sometimes administered in case of initial clear response to alemtuzumab and late occurrence of new relapses and or new T2/Gd enhancing lesions in the MRI.

Statistical analysis

Data are reported as means and standard deviations (SDs) or medians with interquartile ranges (IQRs), according to their parametric or nonparametric distributions. The EDSS scores before alemtuzumab and the score at the last follow-up were compared by nonparametric Wilcoxon signed rank test for paired data. Kaplan–Meier survival curves were used to analyse the time to the first relapse from start of alemtuzumab until the end of follow-up in patients shifting from second-line treatments, versus naïve patients and patients shifting from first-line DMDs considered together. Results with p values of less than 0.05 were considered significant.

Results

Clinical and demographic features

In total, 90 patients were enrolled in this study, as follows: six were enrolled in 2009 in the CAMMS 324 clinical trial, five of whom were actually enrolled in the extension phase of the study (TOPAZ); two received the first course of alemtuzumab in the "free of charge" program between 2014 and 2015; and the other 82 patients were administered the drug after its approval in Italy between 2015 and 2018.

The main clinical and demographical features are shown in Table 1. A third course of alemtuzumab was administered in six patients due to late occurrence of relapses or new/Gd-enhancing lesions, only one patient underwent four courses during a follow-up of 9 years. Within this subgroup with more than two courses of the drug, four of them were originally enrolled in the CAMMS 324 clinical trial.

Among the entire cohort, seven patients were naive to other DMDs, whereas 83 started alemtuzumab after another DMD, with variable washout (Table 2). All patients started alemtuzumab due to failure of the previous DMD, high inflammatory MS without any current DMD, or high risk of PML during natalizumab treatment. The reasons for withdrawal from the previous drug were as follows: inefficacy for 50 patients, AEs for 2 patients, pregnancy or attempt to start a pregnancy for 5 patients, patient's choice for 2

Table 1 Clinical and demographic features of the cohort

Females *n* (%)	67 (74.4)
Age at onset (mean years, SD)	26 (6.9)
Disease duration at alemtuzumab start (mean years, SD)	36 (7.7)
One alemtuzumab course	16
Two alemtuzumab courses	67
Three or more alemtuzumab courses	7

Table 2 Last DMD before alemtuzumab and washout between the two drugs

DMD	Patients, *n* (%)	Washout in months (mean; SD)
None	7 (7.8)	–
Teriflunomide	4 (4.5)	2; 0.8
Glatiramer acetate	5 (5.5)	3.4; 4.8
Fingolimod	20 (22.2)	4.5; 4.1
Interferon beta	10 (11.1)	2.4; 4.4
Mitoxantrone	1 (1.1)	19
Dimethylfumarate	14 (15.5)	2; 1.4
Natalizumab	29 (32.3)	6.8; 9.1
Total	90 (100)	4.6; 6.5

patients, and high risk of PML for 22 patients who shifted from natalizumab. Patients withdrawing from a previous DMD due to pregnancy, own choice, and AEs started alemtuzumab treatment owing to high disease reactivation of MS without therapy, according to AIFA indications. Moreover, one patient enrolled in the CAMMS 324 clinical study shifted from interferon beta to alemtuzumab according to the study protocol. Finally, one patient underwent the complete course of mitoxantrone, starting alemtuzumab treatment after 19 months owing to high reactivation of the disease.

Efficacy: relapses

After alemtuzumab, 22 patients had at least 1 relapse (24.4%). Among patients in this clinically active subgroup, six patients had two relapses and two patients had three relapses. The total number of observed relapses was 32. Eighteen occurred between the first and second courses, 12 after the second course, and 2 occurred after the third course.

The time to first relapse was shorter in patients shifting from second-line DMDs (natalizumab, fingolimod, and mitoxantrone) than that in treatment-naïve patients and in those shifting from first-line DMDs ($p = 0.011$; Fig. 1). The two groups were paired according to sex, age, disease duration, and EDSS score at the start of alemtuzumab.

Efficacy: EDSS

The median EDSS score was significantly reduced from 2.5 (IQR 1.5–4) at the start of alemtuzumab to 2.0 (IQR 1.5–3.5) at the last follow-up ($p = 0.025$). The EDSS score after alemtuzumab decreased in 27 patients (30%), was stabilised in 46 patients (51%), and increased a maximum of 1.5 EDSS points in 17 patients (19%).

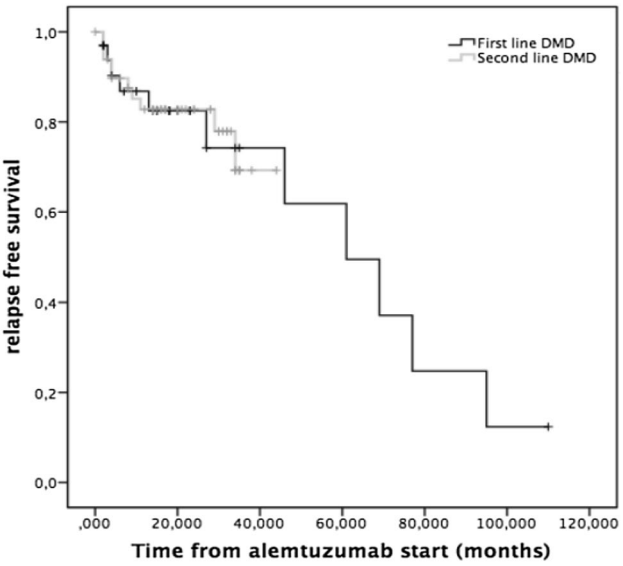

Fig. 1 Time to first relapse according to previous DMD

Efficacy: MRI

Data regarding MRI performed after alemtuzumab treatment were available for 70 patients. Neuroradiological disease activity, either with new T2 lesions or Gd-enhanced lesions, was observed in 23 patients (47.9%) in the first MRI scan after alemtuzumab, performed after a mean of 9.1 months after the first course (SD: 7.6). In eight of these patients, neuroradiological disease activity was also detected in subsequent MRI scans. In the group without activity in the first MRI, new and/or Gd-enhanced lesions were detected in four patients in subsequent scans.

Efficacy: NEDA-3

Considering the cohort of 48 patients with 2-years of follow-up and complete data, including comprehensive MRIs, relapse evaluations, and EDSS scores, 21 patients (43.7%) reached NEDA-3 status. When we excluded from the analysis the disease reactivations occurred between the first and the second course of alemtuzumab, 36 patients (75%) reached NEDA-3 status over 3 years.

Drop-out

Only two patients (2.2%) were considered drop-outs due to the persistence of high inflammatory activity, both clinical and neuroradiological, after the second course of the drug. One of these patients started ocrelizumab treatment in November 2018, 10 months after the last course of alemtuzumab. The other patient is under evaluation for hematopoietic autologous stem cell transplantation.

Safety

All but four patients (95.5%) experienced infusion-related reactions, such as rash, fever, headache, and shivers. During alemtuzumab 10 patients (11.1%) were diagnosed with pneumonitis, and the current course was stopped. In particular, one patient experienced this AE during both courses, five patients experienced this AE during the first course, and two patients during the second course. Only one female patient completed the missing three infusions after the resolution of pneumonitis (approximately 45 days after experiencing the AE). In all patients, the resolution was complete after a multidrug regimen with antibiotics, antiviral agents, antimycotic agents, and steroids. In all cases, the diagnosis was made by a pneumologist after thorax radiography and, in some cases, high-resolution computed tomography. No specific examinations were performed to determine the correct aetiology owing to the lack of availability of these approaches at our hospital.

One infection by *Listeria* was observed in a young patient soon after the first course of alemtuzumab. Evaluation of secondary autoimmune diseases revealed ten cases of thyroiditis (11%) and three cases of thrombocytopenia (PTI; 3.3%). We considered "thyroiditis" both a new diagnosis and a worsening of a previously known autoimmune thyroid dysfunction. The PTI resolved and did not occur in all patients. Two of these patients required a course of intravenous immunoglobulin after steroids, although this treatment was not sufficient for one patient, who started rituximab. The details of these reactions are shown in Table 3. Notably, two female patients experienced both autoimmune AEs. No other secondary autoimmune diseases were observed.

During the follow-up, we observed seven pregnancies in six patients. All patients became pregnant after the second course of alemtuzumab (one after 6 months, one after 8 months, one after 1 year, three after 2 years, and one after 8 years). Three of these patients experienced full-term pregnancies; the infants were healthy, and no AEs or disease exacerbation were observed during pregnancy or the puerperium. Two pregnancies are still ongoing at the time of preparing this report. For the two pregnancies that started after 6 and 8 months from the second course of alemtuzumab, the patients experienced miscarriages at weeks 4 and 6. One of these patients had a known diagnosis of type 1 diabetes, and in both cases thyroid dysfunction was observed during the months before or after the miscarriage.

Discussion

In this study, we described the efficacy and safety of alemtuzumab in a cohort of 90 patients with RRMS. The single-centre design of the study was important to ensure high homogeneity of procedures, and all neurologists had high expertise in MS and followed centre-specific guidelines for the treatment of MS. All patients started alemtuzumab according to AIFA indications. In particular, approximately 25% of our cohort shifted from natalizumab to alemtuzumab owing to the high risk of PML, most patients had failed other DMDs, and the baseline disability was low.

During follow-up, approximately 75% of patients had no relapses, and this finding was quite similar to the percentage of relapse-free patients in both the CARE-MS I and CARE-MS II clinical trials (78% and 65%, respectively) [4, 5], and in a recent real-world observational study (75%) [20]. The majority of relapses recorded in our study were observed between the first and second courses of alemtuzumab, and they could not be ascribed to drug inefficacy, being the complete treatment composed by two courses. In two cases, clinical reactivation after the second course was considered particularly serious and was also found to be associated with high inflammatory MRI activity; thus, in these cases, the drug was considered not efficacious.

Table 3 Time of occurrence of secondary autoimmune diseases

Patient *n*	Setting	Thyroiditis	Thrombocytopenia
1	RW	11 months after the 1st course	11 months after the 2nd course
2	RW	11 months after the 1st course	–
3	RW	3 months after the 2nd course	–
4	CT	10 months after the 2nd course	–
5	CT	19 months after the 2nd course	–
6	RW	19 months after the 2nd course	–
7	CT	17 months after the 2nd course	–
8	CT	46 months after the 2nd course	44 months after the 2nd course
9	RW	7 months after the 2nd course	–
10	RW	12 months after the 2nd course	–
11	CT	–	13 months after the 4° course

CT clinical trial, *RW* real-world

Notably, when comparing patients shifting from second-line DMDs with the group of treatment-naïve patients and patients shifting from first-line DMDs considered together, the time to first relapse was shorter in the first group. This difference may be related to the role of neuroinflammatory reactivation and the possibility of rebound after some second-line DMDs, as has been documented for natalizumab and fingolimod [23–25]. Moreover, more than half of the cohort stopped therapy with a previous DMD due to inefficacy; thus, we expected to encounter high disease activity at the start of alemtuzumab therapy when the previous DMD was a second-line therapy.

When comparing EDSS scores at the start of alemtuzumab treatment with the last follow-up, we found a significant improvement. Indeed, the score worsened only in 19% of patients for a maximum of 1.5 points and decreased in 30% of the cohort. Similarly, in the CARE-MS I and II trials, the EDSS score improved, and sustained accumulation of disability was found in 8% and 13% of patients, respectively [4, 5]. Our data were also consistent with those of a study by Prosperini et al., who showed that a sustained reduction in disability was found in 27.5% of patients [20].

In our study, approximately half of the cohort showed new T2/Gd-enhanced lesions at the first MRI, performed between the first and second courses of alemtuzumab. This was expected because the patients exhibited highly active disease before the start of treatment or were stable but shifted from natalizumab, which can induce reactivation of the disease. Moreover, alemtuzumab is given in two courses of treatment (the first course of 12 mg daily for 5 days, followed 12 months later by 12 mg daily for 3 days), and we cannot expect a complete response to the drug before the completion of both courses. Only a few patients had MRI activity in scans performed later, and often this activity was low-grade, isolated inflammation.

Owing to the real-world setting of the study and the fact that alemtuzumab was widely used in Italy beginning in 2015, only approximately half of the cohort had complete clinical and MRI data for at least 2 years of follow-up. In this subgroup of patients, we found no evidence of disease activity (NEDA-3) in approximately 44% of patients, which was slightly higher than the percentage of patients with NEDA-3 at over 2 years of follow-up found in the CARE-MS I and II trials (39% and 32%) [4, 5]. However, the percentage in our study was similar to that in a real-world study by Prosperini et al., in which NEDA-3 was reached in 45% of patients at over 3 years of follow-up [20].

Recently, Wiendl et al. proposed a patient classification according to the response to alemtuzumab [26]. They defined type 1 as the best-case scenario, with a durable and complete response from the first course of alemtuzumab; type 2 as a complete but transient response, without reactivation after the first course, but with disease activity after the second course and possible choice of retreatment; type 3 as an incomplete early response, with MS reactivation between the two courses and stabilisation after the completion of treatment; and type 4 as the worst-case scenario, consisting of a primary nonresponse both after the first course and after the second course. In our cohort, considering exacerbation as either a relapse or MRI activity, we classified 51 patients (56.7%) as type 1, 9 patients (10%) as type 2, 24 (26.7%) as type 3, and 6 (6.6%) as type 4. The two patients who dropped out of the study could not be classified according to the same type of response profile. In fact, one had a complete initial response after the first course and reactivation of disease less than 1 year after the second course (type 2); in this case, we did not retreat the patient, and another DMD was started because a new relapse and MRI activity were observed 9 months after the second course. The other patient exhibited clinical and neuroradiological exacerbation both after the first course and after the second course (type 4); thus, she had a clear nonresponse to treatment according to Wiendl et al. [26]. Additionally, some patients classified as type 4 were retreated with alemtuzumab, and some others had neither a new course nor a new DMD. This is because the therapy decision-making in clinical practice is based not only on the presence of disease activity but also on the level of inflammation, the occurrence of both clinical and MRI activity, and the time of exacerbation from the alemtuzumab courses.

As expected from CARE-MS I and II trials, in which 90–97% of patients experienced infusion-related AEs, patients in our cohort also frequently exhibited rash, fever, headache, and shivers during infusions [4, 5]. These AEs had low intensity in most patients and were easily managed in the hospital setting using symptomatic drugs. Interestingly, ten patients received a diagnosis of pneumonitis during the course of alemtuzumab treatment, which was then interrupted. In one treatment-naïve patient, this AE occurred after only two infusions during the first course, and she completed the treatment after the resolution of pneumonitis. In the other nine cases, the AE occurred after at least three infusions during the first course or after two infusions during the second course, and the drug was not restarted due to the neurologist's choice. Patients with pneumonitis during the first course underwent the second course as per protocol, and only one female patient had a second episode. There are no real-world data for other similar cases, if excluding isolated infections with opportunistic agents [23, 27]. Moreover, in the CARE-MS II trial, but not in the CARE-MS I, pneumonitis was reported as an infusion-related AE in only 1% of the population [5]. Unfortunately, a lack of specific diagnostic tools has hampered our knowledge of the causes of these AEs. Recently, a possible cytokine-related aetiology was proposed in a patient with acute pneumonitis and pericarditis during alemtuzumab [28].

Only one opportunistic infection was observed, and no life-threatening diseases have been recorded.

Fewer patients had a diagnosis of secondary autoimmune thyroid dysfunctions than expected from clinical trials. Indeed, although only 11% of our cohort exhibited secondary autoimmune thyroid dysfunction, this condition was noted in approximately 18–19% of patients in the CARE-MS I and II trials [4, 5]. This finding could be explained by the high baseline prevalence of autoimmune thyroiditis in Sardinia, where the study was performed [29]. In fact, many of our patients had a diagnosis of thyroiditis before the start of alemtuzumab and did not experience a worsening after the drug. The percentage of patients with PTI was higher than that in clinical trials (3.3% versus 2.3%) [30]. Nevertheless, this difference was not significant because of the small sample size. Moreover, in the Sardinian population there is a high predisposition to autoimmunity. All patients recovered with sequential treatment specific for PTI, although steroids alone were insufficient for one patient. One patient was treated with alemtuzumab at 3 years after PTI and no recurrence was observed. Autoimmune AEs were often delayed a few years after the last infusion, highlighting the importance of monthly monitoring. Indeed, a risk management plan is crucial for early diagnosis and improved outcomes.

We partially confirmed the safety of the drug with regard to pregnancy outcomes, if pregnancy occurred after the suggested wash-out from alemtuzumab administration. We hypothesise that the two miscarriages observed in this study were related to the concomitant occurrence of thyroid dysfunction, which is a risk factor for miscarriage. Nevertheless, thyroid dysfunction could be an AE related to alemtuzumab, thus the role of alemtuzumab could not be excluded.

The main limitation of our study was also its main strength, i.e., the use of a real-world setting. Indeed, data from real-world cohorts are often less accurate, clinical evaluations are not definitive, data are lacking, and MRI scans are not performed regularly with standardised timing. In particular, an MRI scan after alemtuzumab was not available for all the patients, thus the analysis of MRI data was performed only on a subgroup of them. Moreover, an important outcome as the NEDA could be analysed only in a part of the cohort with complete data and adequate follow-up. Another limitation is the lack of data about relapses before alemtuzumab in our database, thus an evaluation of the relapse rate has not been made.

However, the variability of real-world analysis in our study was limited because all patients were evaluated at a single centre, with shared guidelines between neurologists for the treatment of MS. Another limitation is that the number of patients with long follow-up, which is useful for making conclusions regarding efficacy and long-term safety data, was small. However, the importance of real-world data for confirming efficacy results from clinical trials and improving our understanding of safety profiles in more complex patients and in a "real" setting, such as patients shifting from a second-line DMD, has increased [10]. Post-marketing studies could fill the information gaps derived from premarketing trials, although it is difficult to perform randomised clinical trials in the postmarketing stage, and no postmarketing studies of alemtuzumab have been reported to date [9]. Thus, collection of real-world data from different populations could provide answers regarding the real use of the drug. Recently, an international multicentre study from MSBase was performed comparing alemtuzumab with interferon beta, natalizumab, and fingolimod [31], and other multicentre European studies of alemtuzumab are ongoing [10].

In conclusion, our study confirmed the efficacy of alemtuzumab in a real-world cohort in terms of relapse reductions, EDSS improvement, and decreased MRI activity. AEs were frequent, particularly infusion-related reactions, but could be easily managed. Additionally, secondary autoimmune AEs were manageable with the cooperation of specialised clinicians. The sharing of decision-making and benefit-risk profiles between patients and neurologists is essential, both when the drug is proposed and when an AE occurs. Indeed, patients must know the treatment-related risks, the importance of monthly monitoring, and the possibility of AE management. Our findings provide important insights into these aspects of MS-related treatments and are expected to contribute to decision-making regarding the application of alemtuzumab in the future.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interests about this work.

References

1. Thompson AJ, Baranzini SE, Geurts J et al (2018) Multiple sclerosis. Lancet 391(10130):1622–1636
2. Montalban X, Belachew S, Wolinsky JS (2017) Ocrelizumab in primary progressive and relapsing multiple sclerosis. N Engl J Med 376(17):1694
3. CAMMS223 Trial Investigators, Coles AJ, Compston DA, Selmaj KW et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359(17):1786–1801
4. Cohen JA, Coles AJ, Arnold DL et al (2012) Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380(9856):1819–1828
5. Coles AJ, Twyman CL, Arnold DL et al (2012) Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380(9856):1829–1839
6. Havrdova E, Arnold DL, Cohen JA et al (2017) Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. Neurology 89(11):1107–1116

7. Coles AJ, Cohen JA, Fox EJ et al (2017) Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. Neurology 89(11):1117–1126
8. Willis MD, Robertson NP (2016) Alemtuzumab for multiple sclerosis. Curr Neurol Neurosci Rep 16(9):84
9. Gerardi C, Bertele' V, Rossi S et al (2018) Preapproval and post-approval evidence on drugs for multiple sclerosis. Neurology 90(21):964–973
10. Ziemssen T, Thomas K (2017) Alemtuzumab in the long-term treatment of relapsing-remitting multiple sclerosis: an update on the clinical trial evidence and data from the real world. Ther Adv Neurol Disord 10(10):343–359
11. Maniscalco GT, Cerillo I, Servillo G et al (2018) Early neutropenia with thrombocytopenia following alemtuzumab treatment for multiple sclerosis: case report and review of literature. Clin Neurol Neurosurg 175:134–136
12. Hoffman BM, Zeid NA, Alam U et al (2019) Lambert–Eaton myasthenic syndrome associated with alemtuzumab administration. Mult Scler Relat Disord 27:131–132
13. Ranganathan U, Kaunzner U, Foster S et al (2018) Immediate transient thrombocytopenia at the time of alemtuzumab infusion in multiple sclerosis. Mult Scler 24(4):540–542
14. Madeley J, Hodges G, Birchley A. Development of acquired haemophilia A in a patient treated with alemtuzumab for multiple sclerosis. BMJ Case Rep. 2018;2018: bcr-2018
15. Haghikia A, Dendrou CA, Schneider R et al (2017) Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy. Lancet Neurol 16(2):104–106
16. Wehrum T, Beume LA, Stich O et al (2018) Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis. Neurology 90(7):e601–e605
17. Bernard-Valnet R, Pignolet B, Biotti D et al (2018) Unexpected high multiple sclerosis activity after switching from fingolimod to alemtuzumab. Mult Scler Relat Disord 25:216–218
18. Willis M, Pearson O, Illes Z et al (2017) An observational study of alemtuzumab following fingolimod for multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 4(2):e320
19. Tuohy O, Costelloe L, Hill-Cawthorne G et al (2015) Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry 86(2):208–215
20. Prosperini L, Annovazzi P, Boffa L et al (2018) No evidence of disease activity (NEDA-3) and disability improvement after alemtuzumab treatment for multiple sclerosis: a 36-month real-world study. J Neurol 265(12):2851–2860
21. Huhn K, Bayas A, Doerck S et al (2018) Alemtuzumab as rescue therapy in a cohort of 50 relapsing-remitting MS patients with breakthrough disease on fingolimod: a multi-center observational study. J Neurol 265(7):1521–1527
22. Parks NE, Flanagan EP, Lucchinetti CF et al (2017) NEDA treatment target? No evident disease activity as an actionable outcome in practice. J Neurol Sci 383:31–34
23. Clerico M, De Mercanti S, Artusi CA et al (2017) Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab. Mult Scler 23(6):874–876
24. Hatcher SE, Waubant E, Nourbakhsh B et al (2016) Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA Neurol 73(7):790–794
25. Frau J, Sormani MP, Signori A et al (2018) Clinical activity after fingolimod cessation: disease reactivation or rebound? Eur J Neurol 25(10):1270–1275
26. Wiendl H, Calabresi PA, Meuth SG (2018) Defining response profiles after alemtuzumab: rare paradoxical disease exacerbation. Neurology 90(7):309–311
27. Sheikh-Taha M, Corman LC (2017) Pulmonary Nocardia beijingensis infection associated with the use of alemtuzumab in a patient with multiple sclerosis. Mult Scler 23(6):872–874
28. Blasco MR, Ramos A, Malo CG et al (2017) Acute pneumonitis and pericarditis related to alemtuzumab therapy in relapsing-remitting multiple sclerosis. J Neurol 264(1):168–169
29. Sardu C, Cocco E, Mereu A et al (2012) Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. PLoS One 7(3):e32487
30. Devonshire V, Phillips R, Wass H et al (2018) Monitoring and management of autoimmunity in multiple sclerosis patients treated with alemtuzumab: practical recommendations. J Neurol 265(11):2494–2505
31. Kalincik T, Brown JWL, Robertson N et al (2017) Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. Lancet Neurol 16(4):271–281