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Clinical trial

Alemtuzumab treatment of multiple sclerosis in real-world clinical practice: A report from a single Italian center

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ABSTRACT

Background: Alemtuzumab, is a compound approved for highly active MS, and, in Europe, employed after the use of other disease-modifying treatments (DMTs) with an escalation approach or used as a first therapeutic option. The occurrence of secondary autoimmune adverse events and or infections can differ depending on the employed approach.

Objective: To evaluate the efficacy and safety of alemtuzumab in real-world MS population that encompassed patients previously treated with other DMTs.

Methods: 35 patients, treated with alemtuzumab in a single MS Center, were followed for at least 36 months. The study investigated the prevalence of patients reaching the phase of the non-active disease (NEDA-3). All the adverse events were also reported, and correlations assessed.

Results: At the 36-month follow-up, 66,7% of patients achieved the NEDA-3 status, 90,5% of the patients were relapse-free, 85,7% showed no signs of disability progression, nor signs of MRI activity. Adverse events were observed in 45,7% of the patients and ranked as severe in 23% of them. Cases of autoimmune hemolytic anemia (AIHA), pancytopenia, viral hepatitis E, and noninfectious meningo-encephalomyelitis were found and reported. For these complications, the post hoc analysis showed possible interactive factors and causality related to previous DMT treatments.

Conclusions: In a real-world MS population like the one investigated in our study, alemtuzumab was found to be an effective treatment when employed as an escalation or rescue therapy. The compound exhibits a variable safety profile and frequent adverse events that are likely depending on previous treatments and their impact on the immune system.

1. Introduction

Alemtuzumab (Lemtrada®, marketed by Genzyme) is a humanized anti-CD52 monoclonal antibody licensed in over 70 countries for the treatment of active Relapsing-Remitting Multiple Sclerosis (RRMS). The efficacy and safety of alemtuzumab in RRMS have been evaluated in one phase 2 (CAMMS223; ClinicalTrials.gov identifier: NCT00050778) and two phase 3 studies [CARE-MS I (NCT00530348) and CARE-MS II (NCT00548405)] (Devonshire et al., 2018; Wray et al., 2018). In CARE-MS I and II, alemtuzumab showed improved efficacy when compared to the administration of subcutaneous interferon beta 1 a. In the trial, the compound reduced the frequency of relapses occurring over two years, the number of T1 Gd+ lesions or T2 new and/or enlarging lesions. In CARE-MS II, alemtuzumab also reduced the rate of brain volume loss and 6-month disability progression. In CARE-MS I, the compound failed to produce statistically significant differences for this outcome (Cohen et al., 2012; Coles et al., 2012). In the open-label extension study, a trial that included MS patients who have participated in all the 3 CARE-MS studies, the efficacy in terms of clinical and MRI outcomes was confirmed and maintained for over six years. Of note, more than half of the patients enrolled in the CARE-MS studies did not receive additional alemtuzumab courses nor had other disease-modifying treatment, thereby indicating the high efficacy of the compound. In the majority of the patients, the pre-existing disability remained stable or decreased (Ziemssen and Thomas, 2017).

Alemtuzumab is a potent immunosuppressant that causes profound

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and prolonged B- and T-lymphocyte depletion; unfortunately, it also enhances the risk of infusion-associated reactions, infections and secondary autoimmune disorders that include thyroid disorders (with a cumulative incidence over 6 years equal to 42%), immune thrombocytopenia (ITP) (with a cumulative incidence of 2,3%) and glomerular nephropathies (with a cumulative incidence of 0,27%) (Devonshire et al., 2018; Ziemssen and Thomas, 2017). Devonshire and coll., have proposed recommendations for the monitoring and management of autoimmune adverse events associated with alemtuzumab treatment (Devonshire et al., 2018). The autoimmune complications reached their incidence peak in the third year of treatment. For this reason, periodic monitoring of the phenomenon is needed for at least four years after the administration of the last alemtuzumab dose. Non-ITP autoimmune cytopenias have also been described in MS patients treated with alemtuzumab (Jones and Coles, 2014; di Ioia et al., 2018). The incidence of autoimmune hemolytic anemia (AIHA; 0,05%) and pancytopenia (0,10%), as reported in post-marketing surveys, is lower than what found in clinical trials. The incidence of neutropenia was instead higher in post-marketing settings (0,48%) compared to clinical trials (0,2%) (Ziemssen and Thomas, 2017). Case reports of acquired hemophilia A have also been previously described (Pisa et al., 2018; Madeley et al., 2018; McCaughan et al., 2017)

The cause of autoimmunity due to alemtuzumab is not entirely understood and likely related to the pattern of T- and B-cells repopulation that occurs after their depletion. T-cells repopulation may occur through two pathways: (1) thymopoiesis and (2) the homeostatic proliferation of cells that have escaped depletion. Autoimmune diseases are primarily caused by homeostatic proliferation (McCaughan et al., 2017). Indeed, in individuals with a genetic predisposition to autoimmunity, like MS patients, secondary autoimmune disorders could be triggered by the increased number of autoreactive B-cells that occurs upon lymphocyte repopulation (Jones et al., 2013).

In the CARE-MS I and II studies, when compared to interferon beta 1 a, infections were found to appear more frequently in patients treated with alemtuzumab, reaching their peak of incidence in the first year of treatment (56–63%) but declined to 35–43% in the sixth year. The rate of severe infections per year was rare (< 2% in CARE-MS I and < 3% in CARE-MS II) (Wray et al., 2018; Ziemssen and Thomas, 2017). The most frequent infections described in post-marketing surveillance were produced by *Listeria monocytogenes* (0,26%), a strain that has also been associated with septicemia and meningitis as well as by *Cytomegalovirus* (0,13%) (Wray et al., 2018). A single case of sepsis and pneumonia triggered by *Nocardia beijingensis* occurred in a patient after the first alemtuzumab course. No cases of progressive multifocal leukoencephalopathy (PML) have been reported. A single fatal case of PML was reported in a patient who had switched from natalizumab to alemtuzumab. However, the retrospective analysis of the MRI data indicated that the event was likely due to carry-over PML (Ziemssen and Thomas, 2017; Baker et al., 2017). Cases of alemtuzumab-driven candidiasis, acute disseminated tuberculosis, and sepsis associated with pancytopenia e neutropenia have also been reported (Wray et al., 2018).

In this study, we investigated the efficacy and safety of alemtuzumab in patients treated in our MS Center from October 2014 to January 2019. These patients were either subjects previously treated with natalizumab who ceased the treatment because of their high risk of PML or non-responders to other DMTs. We believe that the use of alemtuzumab as escalation or rescue therapy may have been a critical factor in promoting the high incidence of adverse events that we have observed in our patients.

2. Material and methods

2.1. Study design

Our observational study aimed at elucidating the efficacy and safety issues of alemtuzumab treatment for MS in real-world clinical practice. To that aim, we collected clinical and MRI data from 35 patients treated with alemtuzumab from October 2014 to January 2019. All patients were affected by RRMS (as assessed by the 2011 revised McDonald criteria) (Polman et al., 2011). Before starting alemtuzumab, patients underwent a washout period tailored to the specifics of the last DMT.

Laboratory exams and chest radiography were performed, before the administration of the first infusion, to exclude active or latent infections. As recommended by the latest protocols (Havrdova et al., 2017), to minimize the severity of infusion-associated reactions (IARs), all patients received the prophylactic administration of antihistamines, antipyretics, and intravenous corticosteroids before the administration of alemtuzumab infusions. To prevent herpetic infections, patients also received an oral prophylaxis course of acyclovir 200 mg twice daily on the first day of each treatment. The regimen was maintained for one month. Patients were monitored for vital signs (blood pressure, heart rate, and body temperature) before, during and for two hours after the infusion period. Patients were monitored with laboratory tests every month as required by the current guidelines for the use of alemtuzumab (Havrdova et al., 2017).

2.2. Endpoints

The study evaluated the percentage of patients reaching NEDA-3 status. The status is defined by (1) the absence of clinical relapses, (2) no signs of MRI activity (in terms of new/enlarging T2 and/or T1 Gd+ lesions), (3) lack of disability progression (Giovannoni et al., 2015). The endpoints were assessed as a combined outcome or single endpoints. The evaluation of the NEDA-3 endpoint and its sub-scores was performed only on patients who we were able to evaluate at least the 36-month follow-up. The proportion of patients showing improvements in sustained disability was also evaluated. Endpoints were assessed by neurologists expert in MS (Berger et al., 2017; Río et al., 2006; Phillips et al., 2011). We also investigated and reported the incidence of relapses, disability progression (evaluated with EDSS), and all the adverse events (including infections and autoimmune disorders).

3. Results

3.1. Patient demographics

The clinical and MRI data are reported in Table 1. The study sample consisted of 35 patients (17 women, 18 men) with RRMS. Patients in the study had a mean age of 43,5 ± 8.2 years (range 29–63), a mean disease duration of 16,9 ± 5.8 years (range 8 months-28 years), a median EDSS score of 4.0 (range 1.0–7.5), a median number of relapses in the prior year of 1 (range 0–3), a median number of Gd-enhancing lesions or new/enlarged T2 lesion in the previous year of 0 (range 0–4). The median number of previous DMTs was 3 (range 1–6) and included beta-interferons, glatiramer acetate, fingolimod, mitoxantrone, cyclophosphamide, teriflunomide, intravenous immunoglobulins, and dimethyl fumarate.

Alemtuzumab was started after an adequate washout period from the last DMT. The median washout period was of 73 days. As shown in Fig. 1a, the last DMT were: natalizumab (n = 26, median washout 70 days), fingolimod (n = 7, median washout 88 days), glatiramer acetate (n = 1, washout 132 days) and teriflunomide (n = 1, washout 94 days). The main reasons for the DMT discontinuation and the switch to alemtuzumab were disease activity (n = 15) or, in the case of patients receiving natalizumab who were positive to serum anti-John Cunningham virus antibodies (n = 20, Fig. 1b), safety concerns for the potential risk of developing PML. Five patients (14,3%) received only the first course of alemtuzumab and they stopped the administration because of the recurrence of disease activity (n = 2) or adverse events (n = 3), 4 patients completed the first cycle and are currently scheduled for a second cycle; 2 patients are scheduled to carry out the third cycle

Table 1
Demographics, clinical and neuroradiological features of the study subjects.

Mean age (range)	43,5 years old (29–63)
Gender	M:F = 18:17
Mean disease duration before alemtuzumab (range)	16,9 years (0,66–28)
N. of previous DMTs, median (range)	3 (1–6)
N. of relapses in the 12 months before alemtuzumab. Median (range)	1 (0–3)
N, of new/enlarging T2 lesions before alemtuzumab. Median (range)	0 (0–4)
N. of Gd + T1 lesions before alemtuzumab. Median (range)	0 (0–4)
EDSS scores before alemtuzumab. Median (range)	4.0 (1.0–7.5)
N.of relapses at the 36-month follow-up. Median (range)	0 (0–2)
N. of new/enlarging T2 lesions at the 36-month follow-up. Median (range)	0 (0–2)
N. of Gd + T1 lesions at the 36-month follow-up. Median (range)	0 (0–8)
EDSS scores at the 36-month follow-up. Median (range)	4.0 (0–7.5)

(Fig. 1c).

3.2. Effectiveness

At the end of the present study (January 2019), 26 of the 35 patients had two alemtuzumab courses, 21 patients completed the 36-month follow-up, 28 patients completed the 24-month follow-up, and 30 patients finished the 12-month follow-up. At the 36-month follow-up, 14 (66,7%) patients have achieved the NEDA-3 status, 19 (90,5%) were relapse-free, 18 (85,7%) were free of disability progression, and 18 (85,7%) did not show signs of MRI-related activity (Fig. 2). We observed 6 (17,1%) relapses, 4 of which occurred between the first and second course and 2 after the second course, MRI activity was detected in 5 (14,2%) patients and disability worsening in 2 (5,7%) patients who have completed 2 alemtuzumab courses and in 2 (5,7%) patients after one course. In 3 patients (11,5%), we observed disability improvement.

Two patients are now scheduled to carry out the third cycle of alemtuzumab, one for the appearance of new T2 lesions at the MRI scan performed two years after the second cycle, the other for clinical and radiological signs of disease reactivation occurring 18 months after completion of the second cycle.

3.3. Infusion-associated reactions

Only one patient (who was treated with a “free-of-charge” protocol available before the drug marketing approval in Italy) experienced severe skin rash and itching and required multiple doses of intramuscular betamethasone and chlorphenamine maleate. In 28/36 patients, IARs were mild to moderate and consisted of skin rashes ($n = 21$), headache ($n = 4$), hyperpyrexia ($n = 2$), myalgias ($n = 2$) and bradycardia ($n = 1$). IARs were managed by slowing the alemtuzumab infusion rate or with the administration of additional doses of paracetamol, steroids, or antihistamines. Skin rashes disappeared after the administration of oral cetirizine and betamethasone, headache, hyperpyrexia, and myalgias receded after the use of paracetamol. All the side effects occurred during the first alemtuzumab course.

3.4. Adverse events

We observed 20 adverse events that occurred in 16 patients (45,7%)

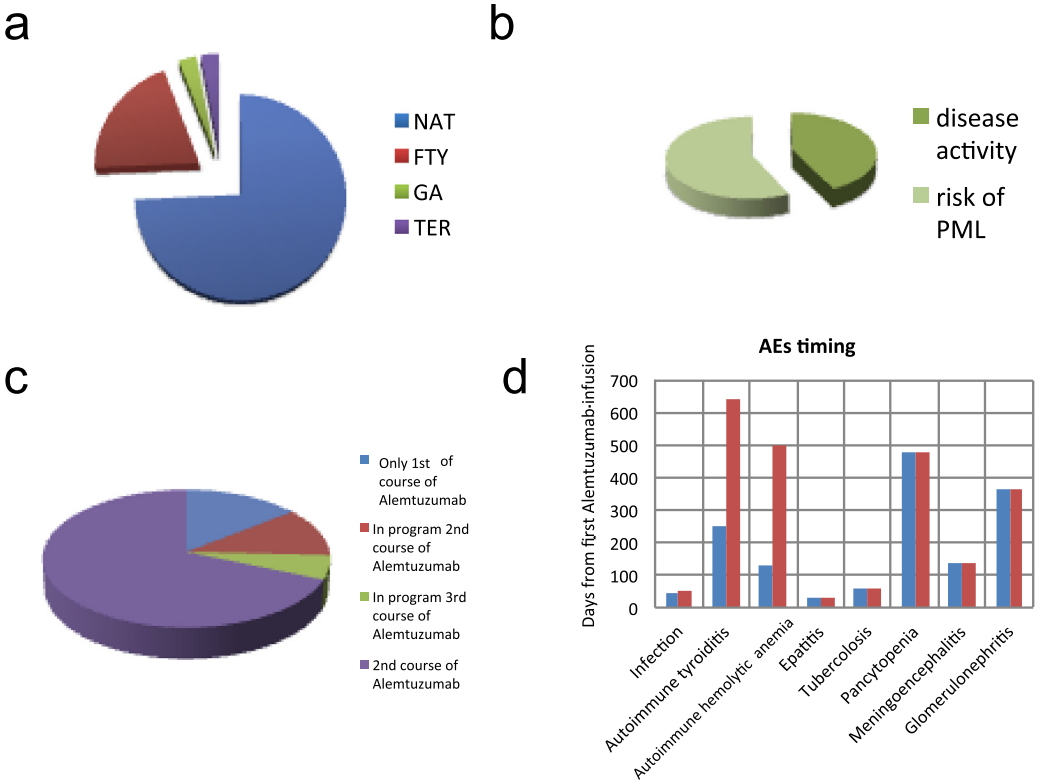

Fig. 1. Panel **a**: Pie chart of the last DMT received before the administration of Alemtuzumab in our cohort: (NAT, $n = 26$), (FTY, $n = 7$), (GA, $n = 1$) and (TER, $n = 1$). **Panel b**: Clinical reasons underlying the decision to activate a DMT vertical switch to alemtuzumab (disease activity 42,9%, safety concerns 57,1%). **Panel c:** Pie chart depicts the distribution of patients who had received the first and the second course of alemtuzumab as well as patients programmed to receive additional courses. **Panel d:** Time frame of the occurrence of adverse events after the first alemtuzumab infusion. The vertical axis indicates the days; the horizontal axis indicates the different adverse reactions. Bars indicate the shorter (BLUE) or longer (RED) time between the infusion of alemtuzumab and the occurrence of the adverse reactions.
Abbreviations: Natalizumab (NAT), Fingolimod (FTY), Glatiramer acetate (GA) and Teriflunomide (TER) DMT, disease-modifying treatment; MS, multiple sclerosis; AEs, Adverse events. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

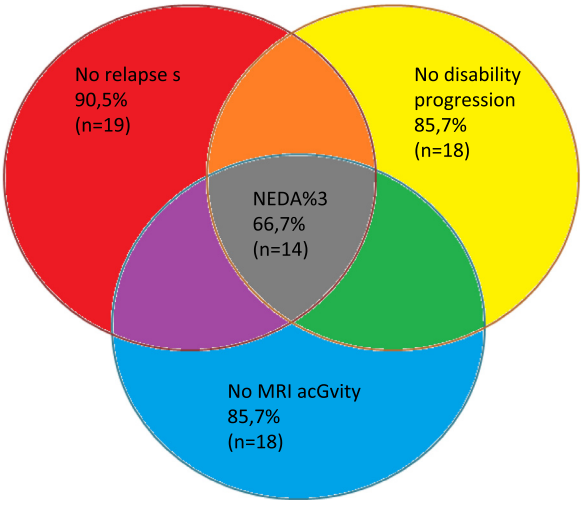

Fig. 2. Percentage of patients achieving the NEDA-3 status and its sub-components at the 36-month follow-up.
Abbreviations: NEDA, no evidence of disease activity.

Table 2
Percentage of adverse events.

Type of adverse events	Number of patients (%)
Thyroid dysfunctions	9 (25,7%)
Autoimmune hemolytic anemia (AIHA)	2 (5,7%)
Pancytopenia	1 (2,8%)
Immune thrombocytopenia (ITP)	1 (2,8%)
Albuminuria	1 (2,8%)
Glomerulonephritis	1 (2,8%)
Cervical intraepithelial neoplasia CIN 3	1 (2,8%)
Viral hepatitis E	1 (2,8%)
Meningo-encephalomyelitis (non-infectious and or non-neoplastic)	1 (2,8%)
Recurrent cystitis	1 (2,8%)

(Table 2, Fig. 1d).

As expected, the most frequent adverse events were autoimmune thyroid dysfunctions (n = 9, 25,7%). 9 of the 20 adverse events (45%) were classified as severe. As for adverse events, we observed 2 cases of AIHA, the first case occurring just before the second alemtuzumab course, while the second case appeared a few months after the second course. The first patient developed AIHA and albuminuria (di Ioia et al., 2018), conditions that were followed three months later by ITP. Several months later, the patient was diagnosed with glomerulonephritis. We also observed a case of pancytopenia and worsening of the neurological status in a patient who had been diagnosed with meningo-encephalomyelitis. The detailed clinical data concerning these severe and unexpected adverse events, as well as their management, are reported in a separate article published in Data in brief. A 49-year-old female patient developed autoimmune thyroiditis and cervical intraepithelial neoplasia (CIN 3). Except for a case of Viral hepatitis E (Hev) and a case of recurrent cystitis, we did not observe other infections. One patient who, before alemtuzumab, had received azathioprine, interferon beta 1a, and fingolimod developed autoimmune thyroiditis. All the other patients who showed adverse effects had been previously treated with natalizumab or other DMTs before natalizumab.

4. Discussion

In this study, we assessed the efficacy and safety of alemtuzumab treatment in real-world clinical practice. Our study population differs from the one investigated in the CARE-MS I and II trials as we included patients with highly active MS who were treated with other DMTs as well as patients treated with natalizumab who had to halt the compound because of their high risk of developing PML. The enrolled patients had a mean age and a mean disease duration higher than the ones enrolled in the CARE-MS II trial. Also, our patients had a higher mean EDSS and a number of previous DMTs (Coles et al., 2012) (Table 1).

At the 36-month follow-up, 66,7% of our patients reached the NEDA-3 status, a percentage that is higher when compared to a previous real-world study (Prosperini et al., 2018) and by the CARE-MS I e II trials (Cohen et al., 2012; Coles et al., 2012). Furthermore, the percentages of all the sub-endpoints were also higher compared to these studies. We found 90,5% of no relapses, 85,7% of no disability progression, or MRI activity (Fig. 2). Interestingly, 14,2% of our patients showed relapses or MRI activity, while disability worsening was found in 5,7% of the patients. In line with previous studies, we observed that most of the relapses and MRI activity occurred 12 months after the first alemtuzumab course (Prosperini et al., 2018). In 11,5% of the patients who had completed two alemtuzumab courses, we observed disability improvement, a percentage lower compared to previous studies. It is conceivable that the phenomenon is due to differences in patient stratification and follow-up length (Coles et al., 2012; Prosperini et al., 2018; Giovannoni et al., 2016). Two of the 21 patients (9,5%) needed to carry out the third cycle of alemtuzumab.

The prevalence of adverse events (45,7% of the patients) was relevant, and in 14,2% of patients caused the cessation of alemtuzumab. In 2 patients, we observed more than one adverse event that co-occurred or happened in sequence. We observed 2 cases of AIHA (5,7%) and 1 case of pancytopenia (2,8%), higher percentages that are supporting the notion that these adverse events may be more frequent in real-world MS population than clinical trials (Ziemssen and Thomas, 2017). The causes of the phenomenon are still not entirely known, but we hypothesize that the previous use of DMTs, particularly immunosuppressant, may modify the immune response and cause secondary autoimmunity. In line with other studies, the most common adverse event we observed was autoimmune thyroid dysfunction (25,7%), whose incidence is likely to increase in the subsequent follow-up (Devonshire et al., 2018; Ziemssen and Thomas, 2017). As for the case of meningo-encephalomyelitis that we describe in the "Data in brief" article, we found that 2 cases of severely exacerbated CNS inflammation with ring-enhancing lesions at the MRI scans, occurring after alemtuzumab treatment have been previously reported (Haghikia et al., 2017). The reports indicated that, like in the case of our patient, the complication occurred several months after the first alemtuzumab course. The authors reported marked improvement after plasmapheresis and rituximab, thereby indicating the likely possibility of an underlying B-cell driven pathological process (Haghikia et al., 2017). In all these cases, including our patient, it remains to be determined whether the complication was due to the worsening of MS or the development of secondary autoimmunity targeting the CNS. Infections were no common in our group of patients, and infusion-related side effects ranged from mild to moderate.

We found, in line with the previous data (Berger et al., 2017), that alemtuzumab can be effectively employed in patients with accumulating disability as a rescue therapy to stabilize the disease and prevent further disability. In all but one of our patients, we prescribed alemtuzumab as escalation or rescue therapy. As indicated in the results section, most of our patients, because of their high risk of PML, had to stop natalizumab treatment or had received other DMTs before natalizumab. These patients had a longer disease duration and a high level of disability when they started alemtuzumab.

We did not find differences in efficacy when comparing patients treated with natalizumab and patients who were treated with fingolimod before alemtuzumab. The reason for halting previous treatments was, in the case of natalizumab, the risk of triggering PML and the possibility of persistent disease activity in fingolimod-treated patients. Our data suggest that alemtuzumab is effective after natalizumab as

well as after fingolimod. Of note, patients in treatment with natalizumab exhibit a highly aggressive form of the disease but remained stable after alemtuzumab, thereby indicating that the drug is an effective alternative to natalizumab and should be considered in patients at risk of PML.

According to a previous study (Malucchi et al., 2017), we found that alemtuzumab is a valid therapeutic option to stabilize the disease and prevent disability worsening in highly active patients, including patients previously treated with natalizumab. As in the previous study (Malucchi et al., 2017), none of our patients, previously treated with natalizumab, experienced PML, but we found that they were more prone to developing adverse reactions. All the adverse events (autoimmune diseases and infections) were observed in patients who have been previously treated with two or more MS-related drugs, including natalizumab. In agreement with Berger et al., 2017, and to obtain more favorable safety and efficacy-related outcomes, we suggest the employment of alemtuzumab as induction therapy or first therapeutic option in young, naive, patients with active disease and low level of disability.

As previously reported (Berger et al., 2017), the alemtuzumab treatment may be more advantageous when early employed in the context of immune systems that are not primed or affected by the use of other DMTs. Furthermore, the employment of aggressive therapy at the beginning of the disease (i.e., induction therapy) may help to promote an immunological reset that leads to more favorable outcomes in terms of being free from disease activity and reducting, long-term, the disease progression. More robust real-world studies are needed to assess the use of alemtuzumab along with the new MS treatments. Pharmacovigilance data originated from clinical practice will likely provide additional information on the real-world efficacy of the compound and help to dissect the safety profiles that may be strongly influenced by factors like the age of the patients, the physiological senescence of their immune systems as well as by the disease duration and previous treatments. Our data indicate that the decision to initiate the alemtuzumab treatment should be carefully assessed for each patient by taking into consideration the individual benefit/risk profile. In general, the risk of adverse events can be mitigated by following the recommendations of the clinical development programs set for the early detection and treatment of adverse events (Havrdova et al., 2017).

5. Ethical standards

All patients gave their informed consent before their inclusion in the study.

6. Funding

The authors declare no financial support for this study.

Declaration of Competing Interest

The authors declare the following potential conflicts of interest regarding the research, authorship, and/or publication of this article: G.D.L. has served as a Bayer, Biogen, Merck, Novartis, Roche, Sanofi/Genzyme, and Teva Advisory Board Member. She received congress and travel/accommodation expense compensations and speaker honoraria from Bayer, Biogen, Merck, Novartis, Sanofi/Genzyme, Teva and Fondazione Italiana Sclerosi Multipla (FISM).; D.F. received congress, and travel/accommodation expense compensations and speaker honoraria from Serono, Biogen, Novartis, Sanofi/Genzyme; D.T. received congress and travel/accommodation expense compensations and speaker honoraria from Roche, Teva, Serono, Biogen, Novartis;

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