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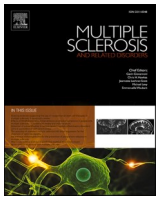

Original article

Acute infusion effects in relapsing multiple sclerosis patients receiving alemtuzumab under a modified prophylaxis regimen

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ABSTRACT

Background: Use of alemtuzumab in relapsing multiple sclerosis (RMS) is limited by safety concerns, notably risk of rare, serious vascular events. Along with other vital sign (VS) changes, acute increase in systolic blood pressure (SBP) is monitored as a marker of vascular risk. Peri-infusion prophylaxis is used to manage clinical risk by moderating cytokine release; protocols are not fully specified and vary across sites. Here, we report a modified prophylaxis regimen developed at Maritime Neurology. This single-center observational cohort study (NCT04633967) aimed to examine acute responses (VS events and infusion-associated reactions) in RMS patients receiving alemtuzumab infusion under this regimen. In a post hoc analysis, we examined incidence of acute SBP increase at this clinic versus the Bayshore network of Canadian infusion centers, where a standard prophylaxis regimen is used.

Methods: Alemtuzumab was infused on 5 consecutive days (Course 1; $n = 29$) and 3 consecutive days one year later (Course 2; $n = 28$). In addition to intravenous methylprednisolone 500mg on each infusion day, patients received daily prophylactic treatment with oral prednisone 50mg from 5 days before to 5 days after treatment (infusion days excepted) and oral H1 and H2 antihistaminics from 7 days before to 7 days after treatment. Excursions in SBP and other VS were relative to prespecified ranges; persistent excursions were those for which two sequential measurements were outside these ranges. In comparing VS events at Maritime Neurology and the Bayshore centers, acute SBP increase was defined as ≥20 mmHg increase in mean SBP, or any SBP reading ≥20% over patient's pre-course baseline.

Results: Mean (SD) VS were within range at pre-course and all other daily baselines. VS changes, including persistent excursions, were generally subclinical; all infusion-associated reactions were mild. One patient discontinued treatment after Course 1 due to immune thrombocytopenia purpura. Acute SBP increase occurred in 11/28 (39%) Maritime Neurology versus 367/610 (60%) Bayshore ($p = 0.028$).

Conclusion: The modified peri-infusion prophylaxis regimen was well tolerated and may reduce incidence of acute SBP increase.

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1. Introduction

Treatment with alemtuzumab rapidly depletes circulating T and B cells, with lesser effects on other CD52-bearing cell lineages (Genzyme, 2021; Cohen et al., 2012). In individuals with relapsing multiple sclerosis (RMS), the resulting lymphopenia is transient but can induce long-term suppression of disease activity. With standard treatment, consisting of five sequential daily alemtuzumab infusions in one year

Abbreviations: C1 (C2), Course 1 (Course 2); D1 (D2 – D5), Day 1 (Days 2 – 5); DBP, diastolic blood pressure; HR, heart rate; HS, hemorrhagic stroke; IAR, infusion-associated reaction; OS, oxygen saturation; PSP, patient support program; RMS, relapsing multiple sclerosis; RR, respiration rate; SAE, serious adverse event; SBP, systolic blood pressure; VS, vital sign; VSAE, vital sign adverse event.

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followed by three in the following year, clinical trials in RMS have demonstrated efficacy over 10 years (Coles, 2021; Coles et al., 2021; Giovannoni, 2021; Steingo et al., 2020).

Acute effects observed during alemtuzumab infusion are associated with inflammatory cytokine release (Wing et al., 1996; Coles et al., 1999; Alakhras et al., 2018; Thomas et al., 2016). These include blood pressure (BP) fluctuation and other vital sign (VS) abnormalities, as well as infusion-associated reactions (IARs) (McEwan et al., 2016). In addition, rare serious adverse effects (SAEs) may occur, including neutropenia and secondary autoimmune disorders (Baker et al., 2017; Costelloe et al., 2012; Giarola et al., 2019).

Vascular SAEs (cervicocephalic arterial dissection, pulmonary alveolar hemorrhage (PAH) and hemorrhagic stroke (HS)) have been observed days or weeks after infusion (Hartung et al., 2020; Azevedo et al., 2019; Durand-Dubief et al., 2019; Holmoy et al., 2019; Vermersch et al., 2020) These vascular events are presumed to arise from cytokine exposure or cytokine-driven hypertension (Libertinova et al., 2021). Thus, the cytokine response necessitates careful monitoring of patients during and after infusion (Genzyme, 2021) and may limit use of alemtuzumab for RMS (Hartung et al., 2020; Azevedo et al., 2019). Azevedo et al. (2019) have suggested criteria for acute systolic blood pressure (SBP) increase that might help identify patients at risk of hemorrhagic stroke.

To ameliorate the effects of acute cytokine release, alemtuzumab is co-administered with methylprednisolone and with pre- or post-infusion antipyretics or antihistaminics (Genzyme, 2021). Several such prophylaxis protocols have been described, (Chinea et al., 2020; Vukusic et al., 2019; Shosha et al., 2021) but the optimal dosage and timing of these therapeutics remains undefined.

Here, we describe the peri-infusion regimen used since 2016 at Maritime Neurology for all alemtuzumab-treated RMS patients. We report incidence of acute VS changes and infusion-associated reactions (IARs) observed during routine monitoring. In a post hoc analysis, we also compare incidence of acute SBP increases among Maritime Neurology patients, relative to those at Canadian infusion centers using a standard prophylaxis regimen (Bayshore clinics).

2. Methods

2.1. Peri-infusion regimen

Patients received oral histamine receptor H1 and H2 antagonists PO (typically ranitidine 150mg and loratadine 10mg) daily from 7 days prior to infusion to 7 days after. Oral prednisone 50mg was given daily from 5 days prior to infusion to 5 days after, infusion days excluded. Methylprednisolone 500mg was infused prior to alemtuzumab 12mg on each treatment day. Infusions were scheduled for five successive days in Course 1 (C1), followed 1 year later with three successive days in C2.

All RMS patients choosing alemtuzumab treatment provided written informed consent to be treated using this modified peri-infusion regimen. Protocol approval (Advarra IRB, Aurora, Ontario Canada) was granted July 29, 2020.

2.2. VS measurement and IARs

VS, including SBP and diastolic blood pressure (DBP), heart rate (HR), respiration rate (RR), oxygen saturation (OS), and body temperature, were monitored starting immediately before infusion and then each 15 min for first hour of infusion and each 30 min thereafter, until 1 h post-infusion. Persistent VS excursions were those remaining outside the prespecified range (defined in Supplemental Fig. 1) for two sequential measurements. VS adverse events (VSAEs) comprised persistent VS excursions that met criteria for change relative to the patient's pre-course baseline reading.

IARs occurring during or after infusion were documented.

2.3. Comparison with Bayshore patient support program data

Bayshore HealthCare operates infusion centers across Canada, collecting VS data on alemtuzumab-treated patients through their Lemtrada® Patient Support Program (PSP). The Bayshore PSP database, which includes a large, representative set of Canadian RMS patients receiving alemtuzumab, (Morrow et al., 2021) was queried for patients receiving alemtuzumab between May 2014 and October 2019.

For comparisons between Maritime Neurology and Bayshore PSP, the acute systolic hypertension criteria proposed by Azevedo et al. (2019) were used: increase from baseline by $\geq$20 mmHg in daily mean SBP, or any SBP reading $\geq$20% greater than baseline.

2.4. Statistical analysis

Pre-course (C1D1 or C2D1) readings provided baseline VS values. Comparisons of SBP events between Maritime Neurology and Bayshore PSP were by Chi-square.

3. Results

3.1. Patient demographics

Between February 2016 and October 2019, 29 adults received C1 alemtuzumab infusions. The population was predominantly female and had a mean (SD) age of 38.7 (10.0) years (range 22–65) and mean (SD) disease duration of 8.4 (3.5) years (range 2–21). Of 29 patients, 10 had one or more cardiovascular risk factors. Mean (SD) VS values for pre-infusion (Table 1) and infusion day baselines were within limits (Supplemental Fig. 1).

Nine months after the first course of infusions, one patient was diagnosed with immune thrombocytopenia purpura (ITP) and was treated successfully with intravenous immunoglobulins. The patient did not proceed with the planned second course of alemtuzumab. All other patients received a full course of eight infusions in C1 and C2.

3.2. Vital sign excursions during infusion

Overall, mean daily baseline SBP and DBP was stable across infusion days (Supplemental Fig. 1). Mean during-infusion change from baseline fluctuated, ranging from -4 to +4 mmHg (SBP) and from -4 to +1 mmHg (DBP). Nevertheless, persistent BP excursions occurred in some patients on each infusion day. For both SBP and DBP, persistent increases were predominantly <20 mmHg. Incidence of persistent SBP excursions exceeding +20mmHg generally rose during each treatment course. For DBP, persistent increases of this magnitude were rare and only seen in

Table 1
Demographics and baseline vital signs (VS) of Maritime Neurology patients receiving alemtuzumab infusions for relapsing multiple sclerosis.

Baseline characteristic	$N = 29$
Patient sex (n (%) female)	23 (79)
Age (years; mean (SD))	38.7 (10.0)
Duration of multiple sclerosis (years; mean (SD))	8.4 (3.5)
EDSS (mean (SD))	2.9 (1.3)
Cardiovascular risk factors (n (%))	
Hypertension	4 (14)
Type 2 diabetes	1 (3)
Dyslipidemia	2 (7)
Current smoker	5 (17)
Baseline vital signs (mean (SD))	
Systolic blood pressure (mmHg)	122 (16)
Diastolic blood pressure (mmHg)	74 (11)
Body temperature (°C)	36.7 (0.5)
Heart rate (per minute)	70.3 (10.6)
Respiration rate (per minute)	17.4 (1.1)
Oxygen saturation (%)	97.9 (1.4)

C2 (Fig. 1).

Body temperature and HR increases were subclinical and substantially limited to the first day in each course (Supplemental Fig. 2). OS and RR findings were unremarkable at all time points; no acute changes were noted.

Over the 8 infusion days, 15 patients (10/29 in Course 1; 10/28 in Course 2) experienced ≥1 VSAE (Table 2). Episodes of persistent tachycardia (8 episodes in 6 patients) and bradycardia (16 episodes in 9 patients) and of persistent systolic hypertension (5 episodes in 3 patients) are described in Supplemental Table 1. Most were asymptomatic, and many appeared to reflect the patient's pre-infusion history. Thus, all instances of persistent elevated SBP were associated with high daily baseline SBP, and most episodes of persistent bradycardia during infusion occurred in individuals with low pre-infusion HR, related in some cases to a lifelong regimen of vigorous physical exercise.

Most episodes of persistent tachycardia occurred in individuals with high baseline HR and/or a history of anxiety disorders, thus complicating any evaluation of causality. Conversely, in one persistent tachycardia event, presumed to be treatment-related, the patient became flushed and experienced a 70% rise in HR (66 bpm at baseline, rising to 114 bpm by the end of the infusion, returning to 60 bpm one hour afterward).

3.3. Infusion-associated reactions

IARs occurred in 26/29 (90%) patients in C1 or C2 (Table 2). The most frequently observed were headaches (66 episodes in 23 patients), occurring with decreasing frequency across infusion days. All headaches were mild and responded to acetaminophen or NSAIDs. Dermatologic events were also relatively common (31 episodes in 16 patients), with increasing frequency over each course. All dermatological events were mild and were managed with diphenhydramine or infusion-rate reduction. Gastrointestinal events (18 episodes in 12 patients) and less common IARs (dyspnea, flushing, insomnia, pain and sore throat) were likewise mild.

3.4. Comparison with Bayshore infusion clinic patients

In a post hoc analysis, the criteria proposed by Azevedo et al. (2019) for identifying potentially problematic SBP increase were used to compare outcomes at Maritime Neurology versus the Bayshore Clinics, another Canadian organization conducting frequent alemtuzumab infusions in patients with RMS. VS data were available for 829 patients receiving alemtuzumab infusions at the Bayshore clinics. Patients' mean (SD) age (37.0 (8.7) years; range 16–65 years) was comparable to that of alemtuzumab patients at Maritime Neurology.

Among patients with complete SBP data across Courses 1 and 2, Azevedo criteria events occurred in 11 of 28 (39%) Maritime Neurology patients versus 367 of 610 (60%) Bayshore patients ($p = 0.028$). A sensitivity analysis, incorporating all available SBP data from the two datasets, did not meet statistical significance but showed numerically lower incidence of Azevedo criteria events among Maritime Neurology patients (38% vs 54%, $p = 0.087$).

4. Discussion

Peri-infusion prophylaxis helps moderate VS changes and suppress IARs in alemtuzumab-treated patients (Coles et al., 1999; Thomas et al., 2016) The simple prophylaxis regimen employed in this study (NCT04633967) was well tolerated and is generally consistent with product labeling and protocols of relevant clinical trials (Genzyme, 2021; Lemtrada Prescribing information 2022). Canadian labeling calls for pre-infusion premedication with corticosteroids on Days 1-3 of each treatment course; use of methylprednisolone 1000mg is typical and consistent with clinical study procedure. Antipyretics and antihistamines may be considered, but direction on dosage or timing is lacking.

Corticosteroid dosage has been debated in the literature, with some authors proposing high-dose (1000mg) prednisolone on all infusion days to prevent IARs, and others preferring to minimize exposure, to avoid unnecessary immunosuppressive treatment effects (Sega-Jazbec et al., 2017; Thomas and Sega-Jazbec, 2017). The modified regimen reported here calls for a smaller infused methylprednisolone dose (500mg), applied on all treatment days, as well as a pre- and post-infusion course

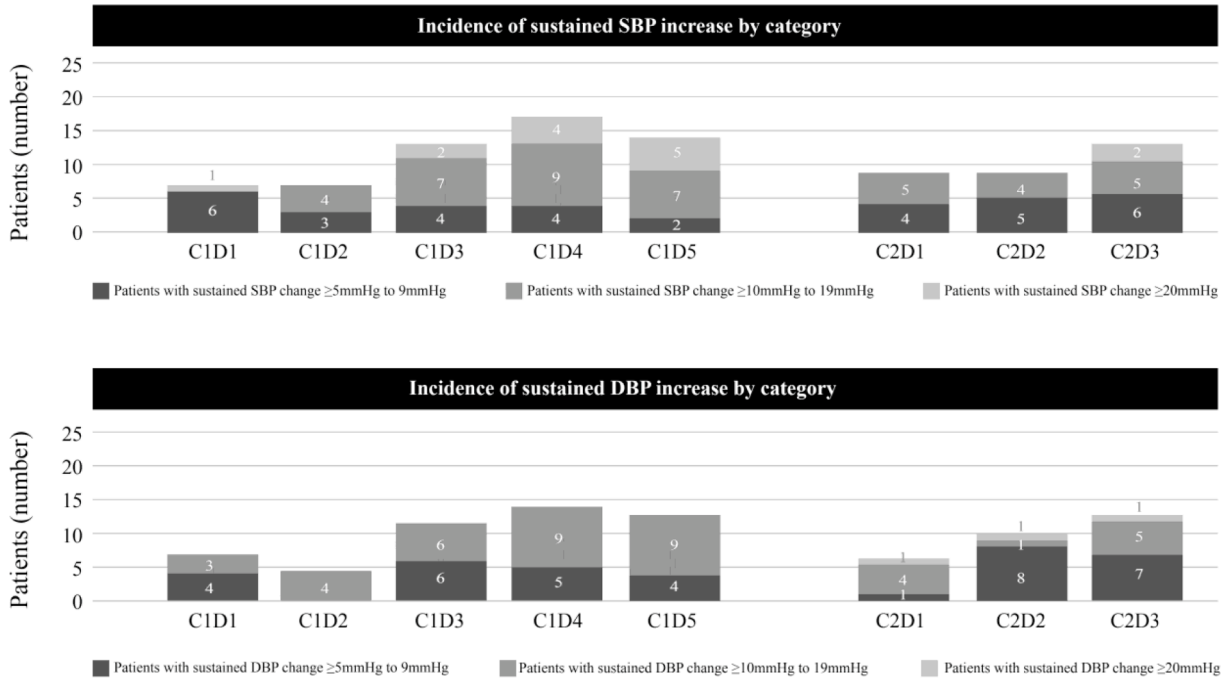

Fig. 1. Number of patients with persistent increase in SBP (above) or DBP (below) by category and infusion day. For Courses 1 and 2, $n = 29$ and 28, respectively. Persistent increases were change over pre-course baseline, maintained over two sequential readings.

Table 2
Persistent vital-sign adverse events (VSAEs; top) and infusion-associated reactions (IARs; bottom) by infusion day. Gastrointestinal IARs included dyspepsia, nausea and upset stomach. Dermatological IARs included rash, pruritus and urticaria.

	Course 1 ($N = 29$)					Course 2 ($N = 28$)		
	Day1	Day 2	Day 3	Day 4	Day 5	Day 1	Day 2	Day 3
Any persistent* VSAE	3 (10%)	2 (7%)	2 (7%)	5 (17%)	6 (21%)	5 (18%)	1 (4%)	4 (14%)
Tachycardia (HR > 100 bpm)	2 (7%)	0	0	1 (3%)	1 (3%)	4 (14%)	0	0
Bradycardia (HR < 50 bpm)	0	2 (7%)	2 (7%)	3 (10%)	3 (10%)	1 (4%)	1 (4%)	4 (14%)
Pyrexia (≥38 °C)	0	0	0	0	0	0	0	0
SBP ≥ 160	1 (3%)	0	0	1 (3%)	2 (7%)	0	0	1 (4%)
SBP ≤95 mmHg with ≥20 mmHg or ≥20% decrease†	0	0	0	0	0	0	0	0
DBP ≥ 110 with ≥10 mmHg or ≥ 20% increase†‡	0	0	0	0	0	0	0	0
DBP ≤ 40 with ≥10 mmHg or ≥ 20% decrease†‡	0	0	0	0	0	0	0	0
Any IAR	14 (48%)	14 (48%)	15 (52%)	16 (55%)	15 (52%)	15 (54%)	14 (50%)	12 (43%)
Headache	12 (41%)	9 (31%)	7 (24%)	8 (28%)	6 (21%)	11	9 (32%)	4 (14%)
Dermatological	1 (3%)	1 (3%)	3 (10%)	6 (21%)	10 (34%)	2 (7%)	4 (14%)	4 (14%)
Gastrointestinal	4 (14%)	3 (10%)	4 (14%)	1 (3%)	1 (3%)	2 (7%)	0	3 (11%)
Flushing	1 (3%)	1 (3%)	3 (10%)	2 (7%)	1 (3%)	2 (7%)	0	1 (4%)
Dyspnea	0	1 (3%)	0	1 (3%)	0	2 (7%)	3 (11%)	1 (4%)
Dizziness	1 (3%)	0	1 (3%)	1 (3%)	0	0	0	0
Insomnia	0	0	1 (3%)	2 (7%)	0	1 (4%)	1 (4%)	0
Pain	0	0	1 (3%)	0	0	0	1 (4%)	1 (4%)
Sore throat	0	0	1 (3%)	0	0	0	0	0

* Persistent events were those meeting VSAE criteria over two sequential measurements. Note that one patient discontinued treatment before initiating Course 2.
† Relative to pre-course baseline.
‡ No DBP event met the AE criteria, irrespective of the requirement for a persistent event.

of oral prednisone and H1- and H2-antihistaminics. Thus, the protocol provides specificity otherwise lacking regarding prophylaxis in RMS patients.

A recent report by Bachmann et al. has also explored lower dose methylprednisone (500mg; all infusion days) (Bachmann et al., 2021). Like these authors, but in contrast to others such as Shosha et al. (2021) we observed no consistent change in mean SBP over time on any infusion day. Daily baseline SBP (and other VS) was consistent during C1 and C2. However, during each course, incidence of persistent SBP excursions ≥+20mmHg increased.

Incidence of IARs in this small study was in line with previous reports, although mild headaches were notably common among our patients, and fever was absent (Cohen et al., 2012; Caon et al., 2015). Minor VS changes during infusion were common and not necessarily drug- or procedure-related, since most persistent SBP and HR excursions reflected fluctuations around the patient's baseline. Conversely, small but statistically significant body temperature and HR increases occurred, substantially restricted to Day 1 of each course. This timing suggests that these VS changes reflect acute increases in cytokine levels following opsonization of CD52 cells by alemtuzumab. The same Day 1-specific pattern of HR and/or temperature increase has been reported previously (Thomas et al., 2016; Chinea et al., 2020; Di Pauli et al., 2022), indicating that it is not specific to the modified peri-infusion regimen.

These and most other observed VS changes were subclinical, likely blunted by prophylaxis, although one patient with normal baseline HR experienced a treatment-related episode of persistent tachycardia. One other patient experienced an autoimmune SAE (ITP) leading to alemtuzumab discontinuation.

Acute SBP increase is proposed as a priority for monitoring, to identify patients at risk of rare vascular events. Azevedo et al. retrospectively analysed five patients experiencing ICH temporally linked to alemtuzumab infusions, whose pathology was consistent with hypertensive etiology (Azevedo et al., 2019; Lemtrada Prescribing information 2021). These authors recommended that alemtuzumab patients be considered high risk for ICH if their mean infusional SBP increases by ≥20mmHg or if any SBP reading rises ≥20% above baseline (Azevedo et al., 2019). While the utility of these criteria has been questioned, (Allen et al., 2020) current EMA guidance on risk management with alemtuzumab identifies infusional BP rise as a potential risk for vascular SAEs (European Medicines Agency, 2021).

We examined incidence of SBP events meeting the Azevedo criteria in the Maritime Neurology population versus a Canadian population from the Bayshore infusion centers, where standard prophylaxis is used. Age structures of the comparator populations were closely matched. The proportion of patients meeting the Azevedo criteria for acute SBP increase was significantly lower by 35% in Maritime Neurology, relative to Bayshore PSP. Hence, the modified peri-infusion protocol used at the Maritime Neurology appears at least as effective as the standard regimen and may be advantageous with respect to SBP excursions associated with ICH.

4.1. *Limitations and strengths*

This small, single-center observational study lacked a comparator arm. The cross-clinic comparison of Maritime Neurology versus Bayshore PSP was a post-hoc analysis and, in the absence of vascular SAEs, necessarily relied on surrogate outcomes. The criteria of Azevedo et al. (2019) which remain the only tool yet proposed to identify alemtuzumab-treated patients at risks of vascular SAEs, stem from a small case series and have not been validated.

One strength of this analysis is the comprehensive VS data set available in the Bayshore PSP records, which, to our knowledge, represent the largest such data set available for alemtuzumab patients. However, anonymization of the Bayshore PSP dataset limited our ability to identify patient characteristics that might confound the analysis of SBP excursions.

5. Conclusions

The peri-infusion prophylaxis regimen described here was well tolerated and can be readily applied elsewhere. VS changes were minor and generally subclinical. All IARs were mild and responded to routine measures. No unexpected safety signals emerged. Larger, comparative studies in diverse populations will be required to establish whether this regimen reduces incidence of SBP excursions or reduces risk of vascular SAEs.

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CRediT authorship contribution statement

Richard Leckey: Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Supervision, Funding acquisition. **Liborio Borsellino:** Conceptualization, Methodology, Data curation, Writing – review & editing, Supervision, Funding acquisition, Project administration. **Andreea M Rawlings:** Methodology, Data curation, Formal analysis, Writing – review & editing. **John Ashkenas:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Amit Suri:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

LB and AS are employees of Sanofi, Canada; AMR is an employee of Sanofi. These three authors may hold shares and/or stock options in the company. RL is a consultant for, and has received honoraria from, Sanofi, Canada, Amylyx, Alexion, Roche, Novartis, EMD Serono, Eli Lilly, and Biogen; JA has no interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104030.

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