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Management of infusion related reactions associated with alemtuzumab in patients with multiple sclerosis

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Hihlights

- Skin reactions and fever were the most common IARs attributed to alemtuzumab infusions.
- Modified premedication scheme may reduce overall IARs associated with alemtuzumab.
- Intravenous compared to oral administration of antipyretics significantly reduces the occurrence of fever.

Abstract

Objective: Infusion-associated reactions (IARs) occur in >90% patients with multiple sclerosis (MS) treated with alemtuzumab. We aimed to study the frequency of IARs at 2 sites using 5 days of steroids (1g/day of IV methylprednisolone), but otherwise distinct protocols.
Methods: This was retrospective chart review of 38 consecutive MS patients who were treated with alemtuzumab from June 2015 till February 2017 at Department of Neurology, University Hospital Center Zagreb, Croatia and Department of Neurology, University Medical Centre Ljubljana, Slovenia.
Results: Seventeen patients (44.7%) did not experience IARs. Skin reactions and fever were the most common IARs attributed to alemtuzumab infusions and they were most frequent on Day 5 and Day 1, respectively. We have observed significant differences in the occurrence of fever (p=0.005) depending on the site of alemtuzumab administration which could be explained by different antipyretics used; fever was absent in the Slovenian cohort because high dose intravenous metamizole was administered. Two out of 9 treatment naïve, and 19 out of 29 patients who previously received immunomodulatory treatment had IARs (χ^2=5.208, p=0.022).
Conclusion: Modified premedication scheme consisting of 1g/day of IV methylprednisolone throughout all 5 days of alemtuzumab treatment may reduce overall IARs. Intravenous administration of antipyretics may work better than oral administration.

Key words: alemtuzumab, infusion associated reactions, multiple sclerosis

Introduction

Infusion-associated reactions (IARs) occur in >90% patients with multiple sclerosis (MS) treated with alemtuzumab, despite all patients receive premedication consisting of 1 g/day IV methylprednisolone immediately before alemtuzumab administration on the first 3 out of 5 days of treatment. (1,2) Furthermore, most physicians use concomitant treatment with antipyretic and antihistamine.

The aim of this study was to study the frequency of IARs at 2 sites using 5 days of steroids (1g/day of IV methylprednisolone), but otherwise distinct protocols.

Methods

This was retrospective chart review of consecutive patients with relapsing remitting MS who were treated with alemtuzumab from June 2015 till February 2017 at Department of Neurology, University Hospital Center Zagreb, Zagreb, Croatia and Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia. All patients received alemtuzumab in outpatient clinic and all adverse events (AE) were recorded on the paper chart and entered in the electronic hospital records. Temperature, blood pressure and heart rate were measured every hour during the infusion, with additional measurements taken if the patient reported new symptoms. Other IARs were spontaneously reported/observed during the infusion visit. AE occurring after the infusion were reported by the patient the next morning and entered in the patient's chart.

IAR were defined as any adverse event beginning during or within 24 hours after an alemtuzumab infusion. Adverse events associated with steroid use (flushing, insomnia, taste changes, elevated blood pressure) were not considered as IARs.

The Croatian cohort received alemtuzumab in an outpatient neurological department, and Slovenian cohort received alemtuzumab in an inpatient neurological department.

Along with his, the need for admitting the patient in the inpatient service was recorded for the Croatian cohort.

Premedication consisted of IV methylprednisolone 1 g / 5 days in all patients. There was a difference in other concomitant treatments, the Croatian cohort received PO acetaminophen 1 g / 5 days and IM chloropyramine 20 mg / 5 days, while the Slovenian cohort received i.v. metamizole 2.5 g / 5 days and i.v. clemastine 2 mg / 5 days. The duration of steroid infusion was 60 min. Other medications were given immediately after steroid infusion and alemtuzumab infusion started 5 min after.

Differences in the distribution of qualitative variables were determined with the χ^2 test, while the differences in quantitative variables were determined with t-test and Mann-Whitney test. P values less than 0.05 were considered as significant. Software used for statistical analysis was IBM SPSS, version 20.

Results

Altogether 38 RRMS patients (20 from Croatia and 18 from Slovenia) were enrolled. Baseline patients' characteristics are presented in Table 1. Alemtuzumab was a 1st therapy in 9 (23.7%), second in 18 (47.4%), 3rd in 9 (23.7%) and 4th in 1 (2.6%) and 5th in 1 (2.6%) patient. Most patients received interferons 20 (52.6%), followed by glatiramer acetate 7 (18.4%), dimethyl fumarate 5 (13.2%), natalizumab 6 (15.8%) and fingolimod 4 (10.5%). For patients switched from interferons, glatiramer acetate and dimethyl fumarate no specific washout period was used. For patients who were switched from fingolimod, the washout period was 6 weeks or until lymphocytes count returned to normal and for natalizumab the wash out period was 12 weeks.

Total number of IARs, timing and frequency of IARs in the two cohorts is provided in Table 2. Skin reactions and fever were the most common IARs attributed to alemtuzumab infusions and they were most frequent on Day 5 and Day 1, respectively (Figure 1). There was a significant difference between groups in the frequency of fever (Table 2).

In the Croatian cohort, in 3 patients IARs resulted in hospitalization, in all 3 cases due to worsening of preexisting neurological deficits associated with fever (in one patient paraparesis and in 2 patients cognitive dysfunction). In the Slovenian cohort in one patient the 5 cycle was administered with a 3 days delay due to rash.

Two out of 9 treatments naïve, and 19 out of 29 patients who previously received immunomodulatory treatment had IARs (χ^2=5.208, p=0.022).

Discussion

With the modification od the premedication given in which we extended methylprednisolone through days 4 and 5, 17 patients (44.7%) did not experience IARs. As well, we have observed a biphasic occurrence of IARs, fever being the most common on the 1st day, and rash being the most common on the 5th day of therapy.

Prevention of alemtuzumab associated IARs is of great importance, as some of IARs (especially fever and skin reactions) may lead to treatment discontinuation. In the CARE-MS

I and II studies, in 45 patients, the first treatment course was suspended/interrupted, and of these, only 24 patients went on to eventually complete their first and second treatment courses. (3)

The most frequently observed IARs in our cohort were skin reactions, occurring in 13 (34.2%) patients, exclusively on days 3 through 5, and peaking on day 5, which is different comparing to 66.1% of patients with skin reactions in the CARE-MS I and II studies (Table 3). (3) This difference could be explained either with higher doses of methylprednisolone or different antihistamines used (the most frequent antihistamines used in CARE-MS I and II studies were diphenhydramine, cetirizine, fexofenadine, hydroxyzine, and loratadine, while we used chloropyramine and clemastine). (3) Similar findings were observed in a recently published study in which authors used methylprednisolone through days 1 to 3 only, and desloratadine and ranitidine as antihistamines, where skin reactions were noticed in 5/15 (33.3%) patients on days 4 and 5. (4) In our cohort, skin reactions resulted in 3 days treatment interruption in only one case.

The second most common IAR was fever, occurring in 7 (18,4%) patients, which is comparable to CARE-MS I and II studies where fever occurred in 23.9% patients. (3) Fever was associated with worsening of previous neurological symptoms in 3 cases, which resulted in admission of patients in the inpatient neurological service. This phenomenon of recurrence of previous MS relapse symptoms, typically lasting a few hours, was previously reported in association with alemtuzumab infusions. (5) Recently, it has been shown that C-reactive protein and procalcitonin peak at serum levels consistent with septic conditions during the first five days of alemtuzumab treatment, which is very important to know in the context of high fever as an IAR. (4) Furthermore, we have observed significant differences between two cohorts in the occurrence of fever. This could be explained by different antipyretics used; fever was absent in the Slovenian cohort where high dosed of intravenous metamizole was administered.

Finally, we have found association between IARs and previous disease modifying treatment. This finding is interesting because recently it has been emphasized how the immediate and long-term consequences of sequential drug use and the optimum order in which they should be used in MS is unclear but may significantly affect efficacy, adverse events, and longer-term immunocompetence. (6) Although this observation is not supported by the results of the CARE-MS I and II studies, there is a significant difference in previous MS medications between two cohorts which can in part explain this. In the CARE-MS II trial, only 15 patients (4%) received natalizumab, and none received fingolimod or dimethyl fumarate. (2) Finally, it

has to be noted that this observation may be related to the infusion site, significantly more of the patients in Croatian cohort had had previous disease modifying treatments.
This study has several limitations, first of all retrospective data collection and relatively small number of patients. However, there is clear lack of postmarketing studies on IARs management in patients with MS receiving alemtuzumab.
In conclusion, modified premedication scheme consisting of 1g/day of IV methylprednisolone throughout all 5 days of alemtuzumab treatment may reduce overall IARs. Intravenous administration of antipyretics may work better than oral administration.

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Tables

Table 1. Baseline patients' characteristics.

	HR cohort (N=20)	SLO cohort N (N=18)	p value
Gender (F/M)	12/8	15/3	0.113
Age (years)	30.5±8.57	31.67±8.21	0.672
First line/other lines	2/18	7/11	0.036*
Disease duration	4.8±2.7	4.6±7.0	0.870
EDSS	3.0 (2.0-6.0)	3.0 (0-6.0)	0.575
Number of relapses in the previous year	1.5 (1-3)	1 (1-3)	0.280

*statistically significant

Table 2. Total number of IARs, timing and frequency of IARs in the two cohorts

	HR cohort (N=20)	SLO cohort (N=18)	p value
Overall AEs			
Any AE	14 (70.0%)	7 (38.9%)	0.054
Day 1	10 (50.0%)	2 (11.1%)	0.010*
Day 2	2 (10.0%)	1 (5.6%)	0.612
Day 3	4 (20.0%)	4 (22.2%)	0.867
Day 4	6 (30.0%)	4 (22.2%)	0.586
Day 5	9 (45.0%)	4 (22.2%)	0.139
Specific AEs			
Fever	7 (35.0%)	0	0.005*
Skin reactions	8 (40.0%)	5 (27.8%)	0.428
Bradycardia	2 (10.0%)	0	0.168
Headache	1 (5.0%)	1 (5.6%)	0.938
Pain	1 (5.0%)	1 (5.6%)	0.938
Fatigue	0	1 (5.6%)	0.285

*statistically significant

Table 3. Comparison in IARs between pooled results of the Croatian and Slovenian cohorts and pooled CARE MS results (3).

	Pooled results of the Croatian and Slovenian cohorts (N=38)	Pooled CARE MS results (N=811)
Fever	7 (18.4%)	194 (23.9%)
Skin reactions	13 (34.2%)	536 (66.1%)
Bradycardia	2 (5.3%)	Not reported
Headache	2 (5.3%)	348 (42.9%)
Pain	2 (5.3%)	39 (4.8%)
Fatigue	1 (2.6%)	64 (7.9%)

Figures

Figure 1. Distribution of fever and skin reactions.

HR – Croatian cohort; SLO – Slovenian cohort.