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HERPES INFECTION RISK REDUCED WITH ACYCLOVIR PROPHYLAXIS AFTER ALEMTUZUMAB

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INTRODUCTION

- Alemtuzumab is a humanized monoclonal antibody that selectively targets CD52, to deplete circulating T and B lymphocytes; lymphocyte depletion is followed by a distinctive pattern of T- and B-cell repopulation[1,2]
- Alemtuzumab showed efficacy superior to subcutaneous interferon beta-1a (SC IFNB-1a) among relapsing-remitting MS (RRMS) patients in the Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) I and CARE-MS II studies
  - In CARE-MS I (NCT00530348), which enrolled treatment-naïve patients, alemtuzumab reduced the relapse rate by 55% (p<0.0001); no significant reduction in sustained accumulation of disability (SAD) was seen (alemtuzumab, 8% vs. SC IFNB-1a, 11%; p=0.22)[3]
  - In CARE-MS II (NCT00548405), which enrolled patients with disease activity despite disease-modifying therapy, alemtuzumab reduced the relapse rate by 49% (p<0.0001) and risk of SAD by 42% (alemtuzumab, 13% vs. SC IFNB-1a, 20%; p=0.0084)[4]
- Notable adverse events (AEs) associated with alemtuzumab in the CARE MS trials included infusion-associated reactions (IARs), infections of predominantly mild-to-moderate severity, and secondary autoimmunity (mainly thyroid disorders and, less frequently, immune thrombocytopenia)[3,4]
- Acyclovir prophylaxis was introduced midway through the CARE-MS trials (in January 2009 for CARE-MS I and December 2008 for CARE-MS II) at the recommendation of the Data Monitoring Committee due to an increase in mucocutaneous herpes infections after alemtuzumab, most often during the first post-treatment month

OBJECTIVE

The aim of this analysis was to evaluate the impact of prophylactic treatment with acyclovir on the risk of herpetic infections during the first month following alemtuzumab treatment

METHODS

Study Design

- CARE-MS comprised two 2-year, global, randomized, open-label, rater- and dose-blinded, head-to-head, active comparator phase 3 trials, in patients with active RRMS (≥2 relapses in prior 2 years with ≥1 relapse in prior year) who were treatment-naïve (CARE MS I) or who had experienced disease activity while on prior therapy (CARE-MS II)[3,4]
- Patients were randomized to receive alemtuzumab (12 mg/day intravenous [IV] once daily on 5 consecutive days at baseline and 3 consecutive days at 12 months) or SC IFNB-1a 44 µg 3 times weekly
  - In CARE-MS II, randomization into a third arm using 24 mg of alemtuzumab was terminated early and findings were deemed exploratory; however, safety findings from this arm are reported here for completeness

Premedication

- Beginning in late 2008, alemtuzumab-treated patients received acyclovir 200 mg twice daily starting on the first day of each alemtuzumab course and continuing for 28 days after the last day
- Patients received methylprednisolone (1 g/day IV) for 3 days at Months 0 and 12 in all treatment arms
- Premedication and symptomatic treatment with antipyretics, antihistamines, histamine H_2-receptor blockers, and anti-emetics were permitted to minimize IARs

Safety

- Analyses were based on pooled data from all available follow-up of all alemtuzumab-treated patients from CARE-MS I and II
- Data from all patients initially treated with alemtuzumab in CARE-MS I and II were analyzed across both studies from the time of first alemtuzumab treatment

RESULTS

- Patients were randomized to alemtuzumab 12 mg (n=822), alemtuzumab 24 mg (n=173), and SC IFNB-1a 44 µg (n=426)
  - The study was completed by 761 patients in the alemtuzumab 12-mg group, 158 patients in the alemtuzumab 24-mg group, and 322 patients in the SC IFNB-1a group
  - Discontinuations from the study due to AEs occurred in 1 patient for alemtuzumab 12 mg, none for alemtuzumab 24 mg, and 6 in the SC IFNB-1a group
- Herpetic infections were reported for 130 patients (16.0%) in the alemtuzumab 12-mg group, 26 patients (16.1%) in the alemtuzumab 24-mg group, and 11 patients (2.8%) in the SC IFNB-1a group
  - The most commonly reported herpetic infections were herpes simplex and herpes zoster infections (**Table 1**)

Table 1. Incidence of Herpes Infections in CARE-MS I and II

Herpes Viral Infection Preferred Term	SC IFNB-1a 44 µg N=389 n (%)	Alemtuzumab 12 mg N=811 n (%)	Alemtuzumab 24 mg N=161 n (%)
Any herpes viral infection	11 (2.8)	130 (16.0)	26 (16.1)
Herpes simplex[a]	7 (1.8)	92 (11.3)	13 (8.1)
Herpes zoster[b]	3 (0.8)	38 (4.7)	12 (7.5)
Varicella	0 (0.0)	2 (0.2)	1 (0.6)
Herpes virus infection	1 (0.3)	2 (0.2)	1 (0.6)
Herpes dermatitis	0 (0.0)	1 (0.1)	0 (0.0)
Cytomegalovirus	0 (0.0)	0 (0.0)	1 (0.6)
Epstein-Barr virus	0 (0.0)	2 (0.2)	0 (0.0)

[a]Includes the preferred terms herpes simplex, oral herpes, genital herpes and herpes simplex ophthalmic.
[b]Includes the preferred terms herpes zoster and herpes zoster multi-dermatomal.
SC IFNB-1a=subcutaneous interferon beta-1a

- Serious herpetic infections occurred in 3 patients treated with alemtuzumab 12 mg (2 cases of herpes zoster and 1 of varicella meningitis) and in 2 patients treated with alemtuzumab 24 mg (2 cases of herpes zoster) compared with none in the SC IFNB-1a group
  - These events were reported as resolved following anti-viral treatment and all 5 patients completed the 2-year study period

- The incidence of herpetic infections during the first month after each treatment course with alemtuzumab 12 mg was lower in patients receiving prophylactic acyclovir compared with patients who did not receive acyclovir (**Figure 1** and **Table 2**)

Figure 1. Incidence of Treatment-emergent Herpes Viral Infections by Month and Prophylaxis Use of Acyclovir During Each Course for the Alemtuzumab 12-mg Treatment Group (left) and the Alemtuzumab 24-mg Treatment Group (right)

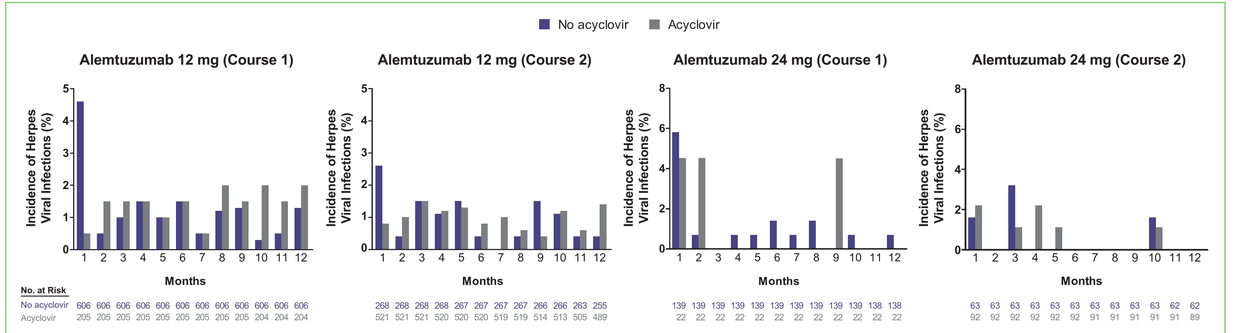

Table 2. Incidence of Herpes Infections During the First Post-treatment Month of Each Alemtuzumab Course in Patients with and without Acyclovir Prophylaxis

	Course 1				Course 2			
	Alemtuzumab 12 mg (N=811)		Alemtuzumab 24 mg (N=161)		Alemtuzumab 12 mg (N=789)		Alemtuzumab 24 mg (N=155)	
System Organ Class Preferred Term	No acyclovir n (%)	Acyclovir n (%)	No acyclovir n (%)	Acyclovir n (%)	No acyclovir n (%)	Acyclovir n (%)	No acyclovir n (%)	Acyclovir n (%)
No. of patients at risk	606	205	139	22	268	521	63	92
Herpes viral infections	28 (4.6)	1 (0.5)	8 (5.8)	1 (4.5)	7 (2.6)	4 (0.8)	1 (1.6)	2 (2.2)
Herpes simplex[a]	27 (4.5)	1 (0.5)	4 (2.9)	1 (4.5)	5 (1.9)	4 (0.8)	0 (0.0)	0 (0.0)
Herpes zoster[b]	1 (0.2)	0 (0.0)	3 (2.2)	0 (0.0)	2 (0.7)	0 (0.0)	1 (1.6)	1 (1.1)
Herpes virus infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Varicella	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Includes the preferred terms herpes simplex, oral herpes, genital herpes and herpes simplex ophthalmic.
[b]Includes the preferred terms herpes zoster and herpes zoster multi-dermatomal. No alemtuzumab patients reported herpes dermatitis, meningitis herpes, or pneumonia herpes viral during the first month after either treatment course.

CONCLUSIONS

- The rates of herpes infections were greater in alemtuzumab patients compared with those in SC IFNB-1a patients in the CARE-MS studies; most were mild to moderate in severity
- Without prophylaxis, risk of herpes infections was highest in the first month of both alemtuzumab 12-mg treatment courses
- Prophylactic treatment with acyclovir for 1 month following each treatment course of alemtuzumab 12 mg was effective in reducing the incidence of herpetic infections

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