Treatment Related Adverse Events Experienced Early and Transiently in the Treatment Course with Cladribine Tablets: Data from the CLEVER Real-World Study

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CONCLUSION

The analysis of the adverse event (AE) occurrence pattern over the observation time of 6 months revealed a higher frequency of AE reports early after treatment initiation.

Cladribine tablets were well tolerated during the first 45 days of treatment as suggested by a relatively low frequency of treatment-related adverse events during this period.

The occurrence of infections was not increased.

Following the 45-day time period the rest of the adverse events were distributed over the remaining observation time with proportionally less adverse events and affected patients.

These observations are in line with the post-hoc analysis of CLARITY and ORACLE-MS safety.

INTRODUCTION

- Cladribine tablets are a short-term treatment approach for patients with highly active relapsing multiple sclerosis (RMS).
- Cladribine tablets are administered over 2 treatment courses in 2 consecutive years with a maximum of 20 days of oral treatment, resulting in a short period of drug exposure.
- The pattern of treatment-related adverse events (AEs) occurrence shortly after start of treatment with cladribine tablets is not yet fully revealed in real-world settings.
- CLEVER (2017-2020) was the first non-interventional study investigating treatment satisfaction with cladribine tablets over 6 months. Here we present data from the safety analysis.

METHODS

- The non-interventional prospective, multicenter study CLEVER was conducted in Germany from 12/2017 to 7/2020 and included adult patients with RMS initiating therapy with cladribine tablets.
- Observation time per patient was 6 months, comprising 3 visits (baseline, week 4 and 24). The occurrence of adverse events was recorded over time.
- The number of treatment-related AEs was assessed and classified based on the last previous MS medication: naïve, platform (interferon beta, dimethyl fumarate, glatiramer acetate, teriflunomide) and high efficacy (alemtuzumab, fingolimod, natalizumab, ocrelizumab).

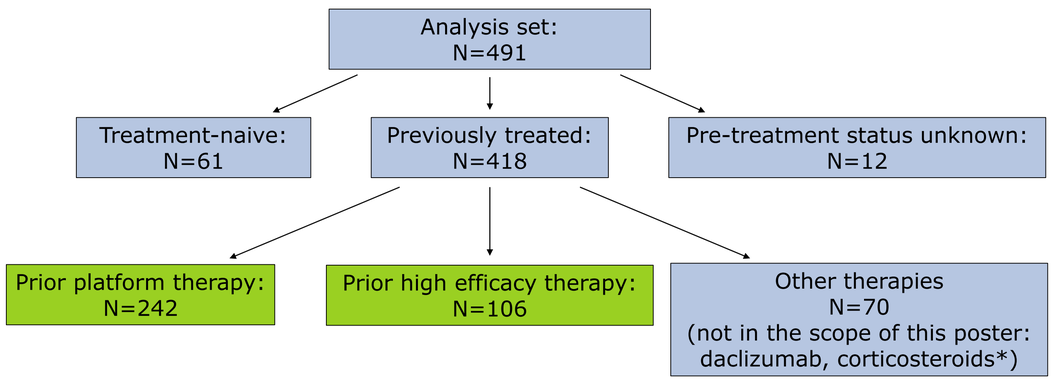
OBJECTIVES

- To investigate the dynamics of safety reporting in a real-world setting and to identify treatment related AE patterns that occur early in the course of treatment with cladribine tablets.

RESULTS

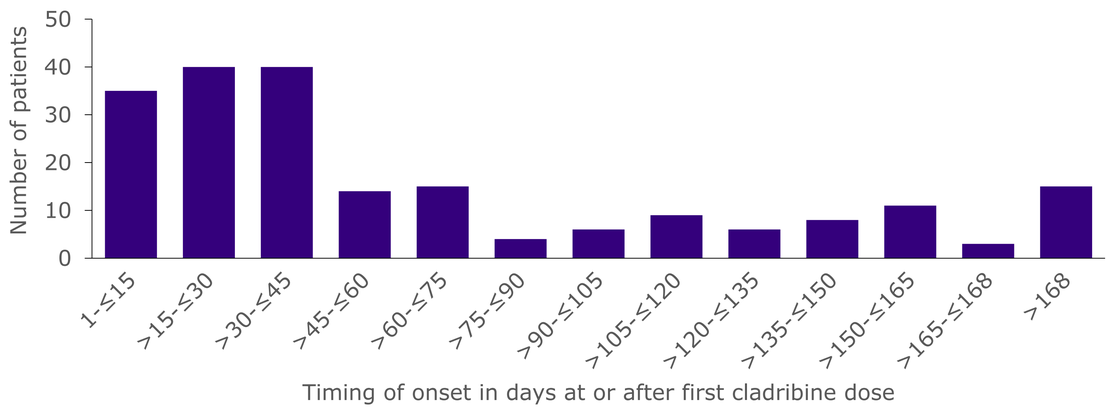
- Out of 504 screened patients, 491 patients initiated therapy with cladribine tablets and were included in the analysis. Furthermore, a classification by last previous therapy was performed (Figure 1).
- Patient demographics for the analysis set are shown in Table 1.
- In the analysis set 187 (38,1%) patients reported AEs (whereby two of these 187 patients experienced AEs between consenting to the study and first tablet intake of cladribine). Treatment-related adverse events (AEs) were reported for 90 patients (18.3%), treatment-related serious adverse events (SAEs) have been reported for 1 patient (0.2%).

Figure 1. Patient flow



*Daclizumab was withdrawn from the market in 2018, corticosteroids are not disease-modifying therapies

Figure 2. Onset of AEs within the given time intervals in the first 6 months



NOTE: 20% of AEs could not be considered for this analysis due to lacking information on exact date of onset (only month provided). Day 1 is the first cladribine intake.

- Among patients experiencing AEs, the substantial proportion (98/185 patients; 53%) had reported AEs within 45 days following first cladribine tablet intake (Figure 2)**
- The most frequent treatment-related AEs within the first 45 days were headache (2.2%), gastrointestinal disorders (2.0%), skin and subcutaneous tissue disorders (1.8%), lymphopenia (1.2%), medication error (1.2%), and fatigue (0.8%) (Table 2).
- Further, the analysis of treatment related AEs by the above defined last previous MS medications within the 45 days' time interval suggested that headache occurred more frequently in platform therapy treated patients, gastrointestinal symptoms as well as skin and subcutaneous tissue disorders in the naïve patients, and lymphopenia in the high efficacy treatment group (Table 2).

**Reports about AEs might emerge from the same patient in time intervals.

Table 1. Patient demographics

	Overall population N=491
Age (years), mean ± SD	40.3 ± 11.5
Females, n (%)	340 (69.2)
Type of MS, n (%) RRMS rSPMS	 458 (93.3) 33 (6.7)
Duration of MS diagnosis (months), mean ± SD	103.5 ± 85.7
Patients with relapses 12 months prior to start of therapy with cladribine tablets, n (%)	343 (69.9)
Number of relapses 12 months prior to start of therapy with cladribine tablets, mean ± SD	1.5 ± 0.7
EDSS, median (IQR)	2.5 (1.5-4.0)
Therapy-naïve, n (%)	61 (12.4)

EDSS, expanded disability status scale; IQR, interquartile range; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; rSPMS, relapsing secondary progressive multiple sclerosis; SD, standard deviation

Table 2. Treatment-related AEs within the first 45 days

	Therapy naive N= 61	Platform therapy N=242	High efficacy therapy N=106	Overall population N=491
Number of patients with at least one treatment-related AE, n (%)	9 (14.8)	17 (7.0)	11 (10.4)	47 (9.6)
Patients with most frequent treatment-related AEs:				
Gastrointestinal disorders, n (%)	2 (3.3)	4 (1.7)	2 (1.9)	11 (2.2)
Headache, n (%)	1 (1.6)	6 (2.5)	2 (1.9)	10 (2.0)
Skin and subcutaneous tissue disorders, n (%)	3 (4.9)	1 (0.4)	2 (1.9)	9 (1.8)
Lymphopenia, n (%)	0 (0)	1 (0.4)	2 (1.9)	6 (1.2)
Medication errors, n (%)	2 (3.3)	1 (0.4)	1 (0.9)	6 (1.2)
Fatigue, n (%)	1 (1.6)	3 (1.2)	0 (0.0)	4 (0.8)

AE, adverse event

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