

Effectiveness and safety profile of cladribine in the long-term in a monocentric real-world population of multiple sclerosis patients

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INTRODUCTION and PURPOSE

The therapeutic scenario for patients affected by Multiple Sclerosis (MS) has enormously increased in recent years, with the availability of various agents with different mechanisms of action. These treatments include cladribine (CLAD), which is a deoxyadenosine synthetic analog prodrug that induces a transient lymphocyte apoptosis and depletion, with only a minimal effect on the innate immune system, followed by an immune reconstitution with improved immune tolerance [1]. CLAD is administered with a short treatment course, thus offering the advantages of a few treatment days per year (8–10 days annually). Despite this, its mode of action is believed to be responsible for a durable clinical effect [2]. Specifically, the current approval of CLAD covers four years, with two treatment courses in the first two years, followed by two treatment-free years. Despite the availability of expert opinion guidance, there is a need for real-world assessment on the efficacy and safety of CLAD in the long term. In particular, the management of CLAD-treated patients beyond year 4 needs to be addressed [3]. We aimed at describing the efficacy and safety of CLAD in a monocentric real-life cohort of relapsing-remitting multiple sclerosis (RRMS) subjects up to 4 years.

METHODS

This is a monocentric, observational, real-world study on relapsing remitting (RR) MS patients treated with CLAD. Relapses, magnetic resonance imaging (MRI) activity, disability, and loss of no-evidence-of-disease-activity-3 (NEDA-3) status were assessed as outcomes. White blood cell, lymphocyte counts and side effects were also evaluated. Patients were analyzed overall and in subgroups according to the last treatment before CLAD. Both patients with MS who started CLAD as first treatment (naïves) and subjects who were previously treated with different disease-modifying treatments (DMTs) (switchers) were considered. We included subjects with a minimum of 6 months of follow-up since CLAD first administration. The relationship between baseline characteristics and outcomes was tested to identify predictors of response.

RESULTS

Two hundred and ninety-five RRMS patients with a median [IQR] follow-up of 27.7 [15.2; 40.5] months were included, of them 141 (47.8%) were treatment-naïve. Main demographic and clinical features included patients are shown in Table 1.

Table 1: Baseline demographic and clinical characteristics of included patients.

	ALL (N=295)	NAIVES (N=141)	1<LINES (N=124)	2<LINES (N=30)	P
Total N (Female N, %)	295 (211, 71.5)	141 (107, 75.9)	124 (88, 71.0)	26 (86.7)	0.201
Age at CLAD start (y), median (IQR)	33.6 (28.3-42.1)	33.7 (28.0-42.7)	33.4 (29.4-41.5)	34.6 (29.1-42.7)	0.880
MS Duration pre CLAD start (y), median (IQR)	3.1 (0.7-9.3)	0.66 (0.3-2.6)	6.4 (3.0-12.3)	8.3 (6.0-14.2)	<0.001
EDSS at CLAD start, median (IQR)	1.6 (1.0-2.0)	1.6 (1.0-2.0)	1.6 (1.0-2.0)	2.0 (1.0-2.9)	0.112
1 year before ARR, estimates (95% CI)	1.4 (1.1-1.5)	3.0 (2.6-3.5)	0.71 (0.5-0.88)	0.7 (0.6-0.9)	<0.001
2 years before ARR, estimates (95% CI)	1.0 (0.9-1.1)	2.6 (2.2-2.9)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	<0.001
Treatment characteristics					
N Previous treatments, median (IQR)	1.0 (0.0-2.0)	-	1.0 (1.0-2.0)	2.6 (2.0-3.8)	
Type of Last Previous treatments, N (%)					
- Naïve	141 (47.8)	141 (100.0)	-	-	
- Interferon	16 (5.4)	-	15 (12.1)	-	
- Glatiramer acetate	20 (6.8)	-	20 (16.1)	-	
- Teriflunomide	16 (5.4)	-	12 (9.7)	-	
- Dimethyl fumarate	71 (24.1)	-	71 (57.3)	-	
- Fingolimod	21 (7.1)	-	-	21 (70.0)	
- Natalizumab	6 (2.0)	-	-	6 (20.0)	
- Ocrelizumab	1 (0.3)	-	-	1 (3.3)	
- Ozanimod	2 (0.7)	-	-	2 (6.7)	
- Immunosuppressants	1 (0.3)	-	1 (0.8)	-	
Presence of new/enlarged brain T2 lesions at rebaseline, N (%)					
	64.0 (21.7)	28.0 (24.8)	29.0 (23.3)	7.0 (23.3)	
Presence of gadolinium-enhancing brain lesions at rebaseline, N (%)					
	26.0 (11.0)	13.0 (11.4)	7.0 (7.1)	6.0 (20.0)	

At 36 months, 84.3% (95% C.I. 79.0–90.0) of subjects were free from clinical relapses; 85.6% (95% C.I. 78.1–93.8) of naïves, 88.5% (95% C.I. 81.3–96.2) of switchers from first-lines and 66.0% (95% C.I. 49.2–88.5) of switchers from second lines (Figure 1). Globally 56.4% (95% C.I. 40.6–78.4) of patients had no MRI activity at 36 months; 56.8% (95% C.I. 37.5–86.1) of naïves, 53.7% (95% C.I. 31.9–90.3) and 48.2% (95% C.I. 23.6–98.4) of switchers from first- and second-line treatments, respectively (Figure 2). Overall, 94.1% (95% C.I. 87.9–100.0) of patients showed no disability progression at 36 months; 98.5% (95% C.I. 95.5–100.0) of naïves, 89.9% (95% C.I. 80.4–100.0) of switchers from first-line and 92.9% (95% C.I. 83.8–100.0) of switchers from second-line treatments (Figure 3). 51.7% (95% C.I. 35.5–79.7) of subjects were NEDA-3 at 36 months; 53.2% (95% C.I. 35.5–79.7) of naïves, 47.0% (95% C.I. 28.7–77.0) of switchers from first-line and 49.8% (95% C.I. 24.4–100.0) of switchers from second-line treatments (Figure 4).

Younger patients were more likely to develop clinical and/or MRI activity and to lose NEDA-3 status during follow-up (all p<0.002). Risk factors for disability progression was an older age at treatment start (p<0.003).

44 patients showed a disability improvement: patients with a lower Expanded Disability Status Score (EDSS) at CLAD start (p=0.008) and naïves (p=0.003) were more likely to show EDSS improvement during follow-up.

52 subjects had 48 months of follow-up and 28 of them started another treatment after CLAD.

Reasons for switching included clinical and MRI activity (28.6%), clinical activity (3.7%), MRI activity (35.7%).

32.1% patients were started on maintenance treatment, despite disease stability.

10/28 subjects performed a third CLAD cycle.

Figure 1: Proportion of patients free from clinical relapses

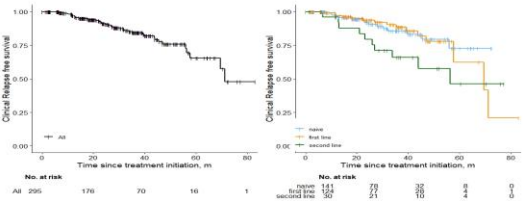


Figure 2: Proportion of patients free from MRI activity

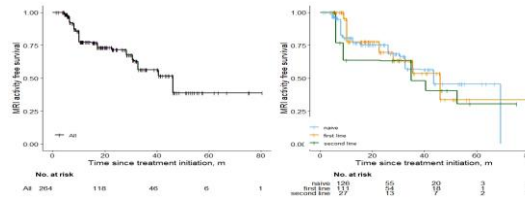


Figure 3: Proportion of patients free from disability progression

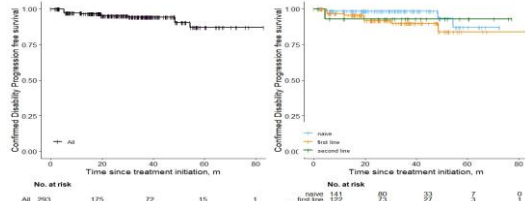
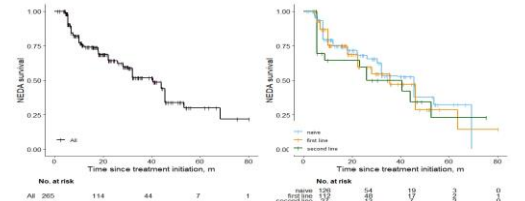
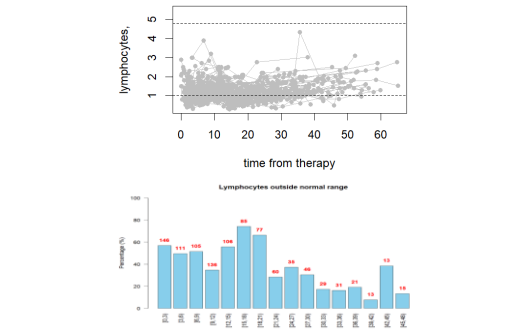


Figure 4: Proportion of patients with NEDA-3 loss



Lymphopenia was still frequent after 15 months (58.5%); the majority of subjects presented grade 2 or 3 lymphopenia and no grade 4 cases were observed (Figure 5).

Figure 5: Longitudinal analysis of non-normal values of lymphocytes



CONCLUSIONS

Our study confirms previous data on CLAD effectiveness and safety. CLAD is more effective when placed early in the treatment algorithm. Real-world data on larger populations are needed to establish treatment algorithms after CLAD in the long term.

REFERENCES

- [1] Giovannoni G et al., Neurotherapeutics 2017
- [2] Zanetta C et al., Journal of Neurology 2023
- [3] Meuth SG et al., Expert Opin on Pharmacotherapy 2022