Early Experience With Cladribine Tablets In An Aging Population

Donald Negroski, MD, Daniel Sellers, PA-C, Amir Khiabani, DO, Devon Khiabani, DO

MS Center of Sarasota (Sarasota, Florida, United States)

BACKGROUND

- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) received US FDA approval in 2019 for the treatment of relapsing forms of MS (RMS; including relapsing-remitting disease and active secondary progressive disease).[1]
- As a chlorinated analogue of deoxyadenosine that is relatively resistant to ADA-mediated deamination, Cladribine preferentially, transiently and selectively depletes CD19+ and CD20+ B cells and, to a lesser extent, CD4+ and CD8+ T cells that have been implicated in multiple sclerosis (MS) pathogenesis.[2-4]
- Cladribine tablets are a short-course oral disease-modifying drug (DMD) administered in four four-to-five-day courses over two years.[5]
- Real-world data can inform therapeutic development, contribute to safety surveillance, and identify patients who will benefit most from a certain treatment.[6,7] Because of this, the effects of cladribine tablets in a cohort of patients from a single clinical center were examined.

OBJECTIVES

Our study aims to present early real-world experience from a single center and to examine a subset of aging MS patients (at least 50 years of age) previously treated with other DMDs switched to cladribine tablets. Understanding the benefit/risk profile of using a non-continuous immunosuppressive DMD in this population is of the utmost importance given immunosenescence and the increased risk of comorbidities with age. Outcomes presented include patient characteristics at treatment initiation, previous DMD use, safety, lymphocyte counts, and preliminary efficacy data.

METHODS

Patients

- Patients ≥18 to 74 years old (n=84) with RMS who received care from the MS Center of Sarasota (Sarasota, FL) and were treated with ≥1 course of cladribine tablets from May 2019 to March 2022 were included in this analysis
- A sub-group analysis was also performed for patients who were ≥50 years of age (n=48) who were treated with cladribine tablets
- Patients with primary progressive MS or clinically isolated syndrome were excluded

Treatment

- The criteria for initiating and continuing therapy with cladribine tablets (3.5 mg/kg) were as followed:
  - 1 or 2 tablets once daily for 4 or 5 consecutive days in months 1 and 2 in year 1
  - 1 or 2 tablets once daily for 4 or 5 consecutive days in months 1 and 2 in year 2
- Dosing is weight based to not exceed 1.75 mg/kg per year
- Patient monitoring was performed in accordance with the US prescribing information[1]

Outcome and Analysis

- Preliminary efficacy was examined by number of relapses, EDSS changes, Annualized Relapse Rate (ARR), and MRI activity before and after cladribine tablets initiation
- Lymphocyte dynamics were measured from baseline through 60 weeks after treatment initiation
- Adverse events (AEs) were recorded using Common Terminology Criteria for Adverse Events version 5.0 (CTCAE)
- Data from patients who did not complete ≥1 treatment course were excluded from the analysis

RESULTS

Patient Characteristics and Prior MS Treatment

- Of 84 patients included in this study, 48 are the Aged ≥50 years subgroup (**Figure 1**)
- Most patients had received 1 or 2 DMTs prior to switching to cladribine tablets (**Figure 2**)
- Factors driving patients to switch to cladribine tablets from their previous DMT included disease progression (new or worsening MRI activity and/or relapse activity), inability to tolerate prior therapy, desire for short-course oral dosing, cost or insurance coverage of previous DMT, JCV positivity, and opportunity for family planning ≥6 months after the final dose of the second treatment course.

Figure 1. Most Recent Treatment Prior to Switching to Cladribine Tablets (All Patients, N=84)

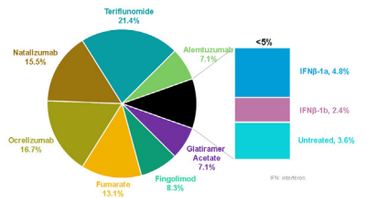
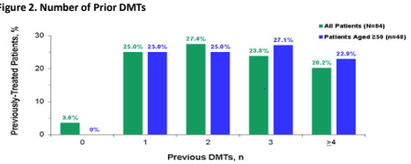


Figure 2. Number of Prior DMTs



- Mean patient age in the overall group was 52.5 years, and 77.4% of patients were female; among the aged ≥50 years subgroup mean age was 60.8 years and 77.0% were female (**Table 1**)
- Mean disease duration was 11.6 years in all patients and 14.7 years in those in the aged subgroup
- Most patients had not experienced a relapse in the 12 months prior to initiating treatment with cladribine tablets

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	MS Center of Sarasota Group[a] All Patients N=84	MS Center of Sarasota Group[a] Patients Aged ≥50 n=48
Age, years		
Mean±SD	52.5±11.6	60.8±6.5
Median (range)	53 (26-74)	61 (50-74)
Female, n (%)	65 (77.4)	37 (77)
Race, n (%)		
White	81 (96.4)	46 (95.8)
Black or African American	1 (1.2)	0
Native Hawaiian or Other Pacific Islander	2 (2.4)	2(4.2)
Disease duration, years		
Mean±SD	11.6±7.8	14.7±7.8
Median (range)	11 (1-31)	14 (2-31)

Table 1. Baseline Demographics and Clinical Characteristics (cont.)

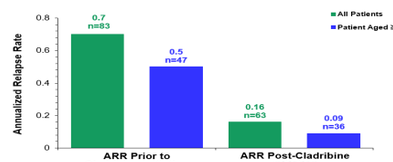
Characteristic	MS Center of Sarasota Group[a] All Patients N=84	MS Center of Sarasota Group[a] Patients Aged ≥50 n=48
Mean ARR (95% CI)	0.7 (0.53-0.87)	0.5 (0.34-0.66)
Relapses 12 months prior to treatment with cladribine tablets, n (%)		
0, n (%)	42 (50.6)	28 (59.6)
≥1, n (%)	41 (49.4)	19 (40.4)
EDSS score		
<6.5, n (%)	69 (84)	35 (76)
≥6.5, n (%)	13 (16)	11 (24)
Patients with T1-Gd+ cranial lesions, n (%)	13 (20.6)	5 (15.2)
Number of T1-Gd+ lesions, mean±SD	0.2±0.5	0.1±0.3
Number of T1-Gd+ lesions, median (range)	0 (0–2)	0 (0–1)

ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; SD, standard deviation. [a] As of March 2022.

Relapse Rates

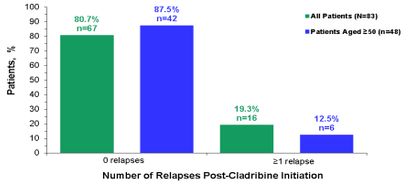
- In the 12 months prior to treatment with cladribine tablets, the Annualized Relapse Rate (ARR) for the All patients group was 0.7 and those in the Patients Aged ≥50 subgroup was 0.5; One year following the initiation of cladribine tablets, the ARR was 0.16 and 0.09, respectively(**Figure 3**)

Figure 3. Annual Relapse Rate Before and After Cladribine Treatment



- Post treatment with cladribine tablets, 80.7% in the All patients group and 87.5% for the Patients Aged ≥50 subgroup were relapse-free (**Figure 4**)

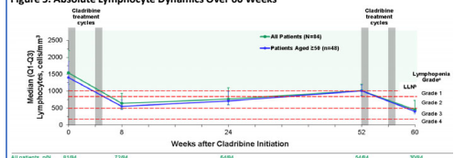
Figure 4. Number of Relapses After Cladribine Treatment



Lymphocyte Dynamics

- Lymphocyte levels decreased rapidly on initiation of the first treatment cycle, reaching nadir at 2 months followed by recovery to normal levels prior to initiation of the second treatment course (**Figure 5**)

Figure 5. Absolute Lymphocyte Dynamics Over 60 Weeks



*Graded according to CTCAE: grade 1, < LLN-800/µL; grade 2, < 800-500/µL; grade 3, < 500-200/µL; grade 4, < 200/µL. †LLN was determined per local laboratory specifications.**LLN**, lower limit of normal; **Q**, quarter.

Adverse Events

- The most common adverse events with an incidence of >5% reported in both groups were lymphopenia, fatigue, upper respiratory tract infection, urinary tract infection, and headache
- Lymphopenia occurred in 89.2% of all patients and 89.6% of patients in the aged subgroup (**Table 2**)
- In year 1, grade 1-3 lymphopenia generally improved over time following nadir at 2 months after treatment initiation (**Table 3**)

Table 2. Adverse Events

Adverse Events, n (%)	All Patients N=84	Patients Aged ≥50 n=48
Lymphopenia	74 (89.2)	43 (89.6)
Fatigue	19 (22.6)	7 (14.6)
Upper Respiratory Tract Infection	13 (15.5)	9 (18.8)
Urinary Tract Infection	11 (13.1)	7 (14.6)
Headache	10 (11.9)	4 (8.3)
Nausea	2 (2.4)	1 (2.1)
Arthralgia and Arthritis	2 (2.4)	1 (2.1)
Back Pain	1 (1.2)	1 (2.1)
Fever	1 (1.2)	1 (2.1)

- 2 serious adverse events were reported: a pneumonia and an asymptomatic fungal lung infection
- In the All Patients Group, 2 patients discontinued treatment due to adverse events, 3 patients discontinued treatment due to disease activity.
- Monitoring for adverse events is ongoing

Table 3. Lymphopenia Following Treatment Initiation With Cladribine Tablets

Lymphopenia[a], n (%)		MS Center of Sarasota Cladribine Group: All Patients Group At Indicated Time Point[b] 0 weeks N=91	8 weeks n=72	24 weeks n=64	52 weeks n=54	60 weeks n=30
Grade 0	≥LLN[c]	73 (90.1)	15 (20.8)	24 (37.5)	31 (57.4)	1 (3.3)
Grade 1	<LLN[c]-800 cells/mm³	2 (2.5)	11 (15.3)	6 (9.4)	14 (25.9)	4 (13.3)
Grade 2	<800-500 cells/mm³	3 (3.7)	26 (36.1)	30 (46.9)	9 (16.7)	9 (30)
Grade 3	<500-200 cells/mm³	2 (2.5)	19 (26.4)	4 (6.3)	0	16 (53.3)
Grade 4	<200 cells/mm³	1 (1.2)	1 (1.4)	0	0	0

Lymphopenia[a], n (%)		MS Center of Sarasota Cladribine Group: Patients Aged ≥50 At Indicated Time Point[b] 0 weeks n=46	8 weeks n=44	24 weeks n=38	52 weeks n=30	60 weeks n=15
Grade 0	≥LLN[c]	39 (84.8)	6 (13.6)	10 (26.3)	16 (53.3)	0
Grade 1	<LLN[c]-800 cells/mm³	2 (4.3)	4 (9.1)	5 (13.2)	9 (30)	0
Grade 2	<800-500 cells/mm³	2 (4.3)	19 (43.2)	22 (57.9)	5 (16.7)	2 (13.3)
Grade 3	<500-200 cells/mm³	2 (4.3)	14 (31.8)	1 (2.6)	0	13 (86.7)
Grade 4	<200 cells/mm³	1 (2.2)	1 (2.3)	0	0	0

[a]Graded according to CTCAE: grade 0, ≥ 1 000/µl; grade 1, < LLN-800/µl; grade 2, < 800-500/µl; grade 3, < 500-200/µl; grade 4, <200/µl. [b]Patients are at different stages of their treatment; therefore, monitoring for lymphopenia is ongoing. cTwo months after initiation of the second treatment course (year 2). dLLN was determined per local laboratory specifications. **LLN**, lower limit of normal.

CONCLUSIONS

- In this cohort of patients initiating therapy with cladribine tablets in a real-world setting, the treatment was well-tolerated.
- There were no new safety signals.
- The side effect profile was consistent with that seen in the clinical trial program, even in an aging patient population where co-morbid conditions and immunosenescence may increase.
- Owing to short follow-up time, it was not possible to assess long-term outcomes.
- Ongoing follow-up will further expand on these results as more patients complete their full treatment course

REFERENCES

1. MAVENCLAD (cladribine) tablets [package insert]. Rockland, MA; EMD Serono, Inc; 2019.
2. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Both cladribine and alemtuzumab may effect MS via B-cell depletion. Neurol Neuroimmunol Neuroinflamm. 2017;4(4):e360
3. Comi G, Cook S, Giovannoni G, et al. Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis. Mult Scler Relat Disord. 2019;29:168-174.
4. Wiendl H, Schmierer K, Hodgkinson S, et al. Characterization of peripheral immune cell dynamics and repopulation patterns in the first 12 months of cladribine tablets treatment: MAGNIFY-MS study. Presented at: American Academy of Neurology Annual Meeting; April 17-22, 2021.
5. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416-426.
6. Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions. US FDA 2021. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence. Accessed October 19, 2021.
7. Franklin JM, Liaw KL, Iyasu S, et al. Real-world evidence to support regulatory decision making: New or expanded medical product indications. Pharmacoepidemiol Drug Saf. 2021;30(6):685-693.

ACKNOWLEDGEMENTS

- Analysis and graphics assistance was provided by MediTech Media, Ltd

DISCLOSURES

- Donald Negroski has received fees as a speaker/consultant from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Inc., Genentech, Janson, Novartis, Sanofi-Genzyme, and TG Therapeutics
- Daniel Sellers has received fees as a speaker/consultant from Biogen, Bristol Myers Squibb, EMD Serono, Inc., and Sanofi-Genzyme
- Amir Khiabani and Devon Khiabani have nothing to disclose

Presented at the 2022 Annual Meeting of the Consortium of Multiple Sclerosis Centers; June 1-4, National Harbor, Maryland

www.PosterPresentations.com