

Analysis of Infection in Younger and Older Patients with Multiple Sclerosis Treated with Cladribine Tablets Who Had Grade ≥ 3 Lymphopenia

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SUMMARY



This study examines infection-related TEAEs in younger (age ≥ 18 – ≤ 50 years) and older (age > 50 – ≤ 65 years) patients treated with cladribine tablets 3.5 mg/kg who experienced Grade ≥ 3 lymphopenia in the clinical development program



Around a quarter of both younger and older patients treated with cladribine tablets 3.5 mg/kg had periods of Grade ≥ 3 lymphopenia at some time during the study



The rate of certain infection-related TEAEs was numerically higher in the older versus younger patients treated with cladribine tablets 3.5 mg/kg who had at least an episode of Grade ≥ 3 lymphopenia



Common infections in patients treated with cladribine tablets 3.5 mg/kg across both age groups were influenza, viral upper RTI, upper RTI, and herpes zoster

Abbreviations: Adj, adjusted; AE, adverse event; DMT, disease-modifying therapy; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IQR, interquartile range; MS, multiple sclerosis; PY, patient years; RTI, respiratory tract infection; SD, standard deviation; TEAE, treatment-emergent AE

References: 1. Leist TP, et al. *Clin Neuropharm* 2011;34:28–35. 2. Comi G, et al. *Mult Scler Relat Disord* 2019;29:168–174. 3. Cook S, et al. *Mult Scler Relat Disord* 2019;29:157–167. 4. Giovannoni G, et al. *N Engl J Med* 2010;362:416–426. 5. Mills EA and Mao-Draayer Y. *Mult Scler* 2019;24:1014–1022. 6. Schweitzer F, et al. *Curr Opin Neurol* 2019;32:305–312. 7. Giovannoni G, et al. *Mult Scler*. 2018;24:1594–1604. 8. Leist T, et al. *Lancet Neurol*. 2014;13:257–267.



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BACKGROUND INFORMATION

- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are an oral DMT, with short and infrequent treatment courses, indicated for relapsing forms of MS
- Cladribine preferentially reduces circulating B and T lymphocytes that are involved in the pathogenesis of MS^{1,2}
 - Given the drug's mechanism of action, reductions in lymphocyte count are expected in patients treated with cladribine tablets^{1,3}
 - In the pivotal Phase 3 CLARITY study, Grade ≥ 3 lymphopenia occurred in 25.6% of patients treated with cladribine tablets 3.5 mg/kg versus 0.5% of those treated with placebo; however, the occurrence of lymphopenia leading to treatment discontinuation was low (0.9% vs. 0%, respectively)⁴
- In an integrated analysis of clinical trials, the rate of infection-related TEAEs was higher in patients treated with cladribine tablets 3.5 mg/kg during periods of Grade ≥ 3 lymphopenia compared with outside of these periods (57.53 vs. 24.50 Adj-AE per 100 PY, respectively)³
- Lymphocyte levels are typically lower in older versus younger patients with MS, and the use of DMTs that further reduce lymphocyte function might therefore be expected to increase the risk of infection-related TEAEs in older patients^{5,6}
- As aging affects immune response, and severe lymphopenia increases the risk of infections, further analyses are needed on the nature of infection-related TEAEs in older and younger patients treated with cladribine tablets 3.5 mg/kg who experienced Grade ≥ 3 lymphopenia

Abbreviations: Adj, adjusted; AE, adverse event; DMT, disease-modifying therapy; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IQR, interquartile range; MS, multiple sclerosis; PY, patient years; RTI, respiratory tract infection; SD, standard deviation; TEAE, treatment-emergent AE

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OBJECTIVE

To examine infection-related TEAEs in patients treated with cladribine tablets 3.5 mg/kg who experienced Grade ≥ 3 lymphopenia by age category (≥ 18 – ≤ 50 and > 50 – ≤ 65 years)



METHODS

- This *post hoc* analysis included data from patients treated with cladribine tablets 3.5 mg/kg in the drug's clinical development program (Phase 3 CLARITY, CLARITY Extension and ORACLE-MS studies)^{4,7,8}
- The rate and type of infections in patients treated with cladribine tablets 3.5 mg/kg who had Grade ≥ 3 lymphopenia during the 96-week treatment period was described by age at baseline (≥ 18 – ≤ 50 vs. > 50 – ≤ 65 years)
- Recovery from an episode of Grade ≥ 3 lymphopenia was defined as a return to Grade ≤ 2
- Infection-related TEAE rates were expressed in Adj-TEAE per 100 PY



RESULTS

- This study included 923 patients treated with cladribine tablets 3.5 mg/kg
- Baseline characteristics were generally well balanced between age groups^a
- At baseline, compared with the Age ≥ 18 – ≤ 50 group, the Age > 50 – ≤ 65 group had^a:
 - A higher proportion of women
 - Longer disease duration
 - Larger proportion of patients with one relapse at baseline
 - Larger proportion of patients with no T1 Gd+ lesions, but with ≥ 9 T2 lesions

Baseline patient characteristics

	Cladribine tablets 3.5 mg/kg	
	Age ≥ 18 – ≤ 50 years (N=813)	Age > 50 – ≤ 65 years (N=110)
Age, years, mean (SD)	34.7 (8.4)	54.6 (3.7)
Female, n (%)	531 (65.3)	81 (73.6)
Disease duration, years, median (range)	6.6 (0.3–32.8) ^b	11.4 (0.4–42.3) ^c
Prior use of DMT		
No DMTs	650 (80.0)	89 (80.9)
1 DMT	128 (15.7)	16 (14.5)
≥ 2 DMTs	35 (4.3)	5 (4.5)
Number of relapses at baseline, n (%)		
0	382 (47.0)	37 (33.6)
1	305 (37.5)	58 (52.7)
≥ 2	126 (15.5)	15 (13.6)
EDSS, median (range)	2.0 (0–6.5)	3.5 (0–6.5)
Number of T1 Gd+ lesions, mean (SD)	1.2 (3.4) ^d	0.3 (1.0)
No lesions, n (%)	524 (64.5)	95 (86.4)
≥ 1 lesion	288 (35.5)	15 (13.6)
Number of T2 lesions, mean (SD)	30.1 (22.3) ^d	26.2 (13.3)
< 9 T2 lesions, n (%)	104 (12.8)	6 (5.5)
≥ 9 T2 lesions, n (%)	708 (87.2)	104 (94.5)

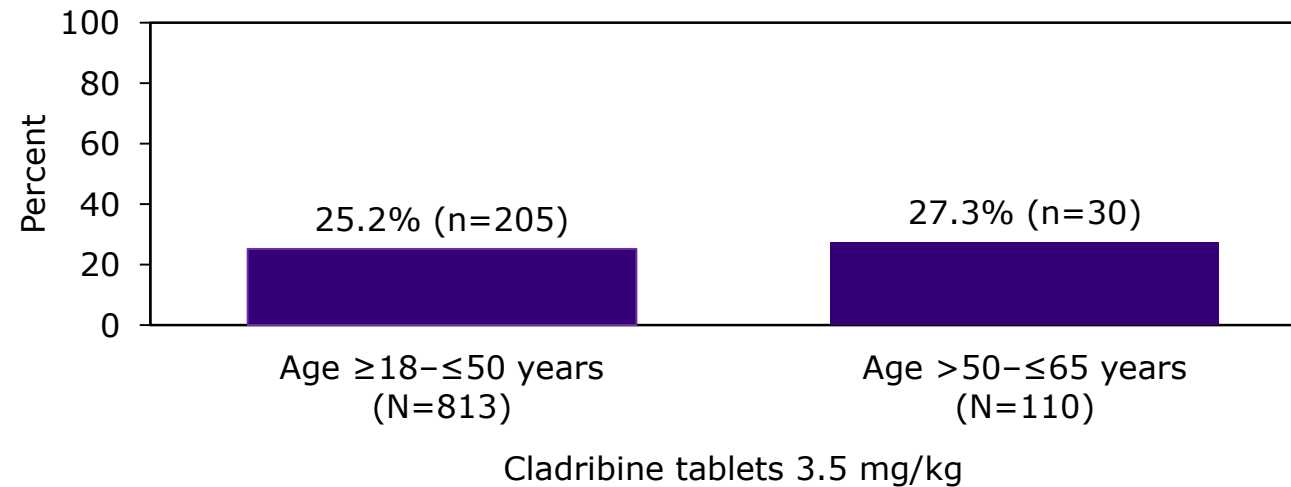
^aStatistical testing to examine differences in the two age groups was not conducted due to multiplicity and low sample size. ^bn=582; ^cn=103; ^dn=812



RESULTS

- In patients treated with cladribine tablets 3.5 mg/kg, 25.2% in the Age ≥ 18 – ≤ 50 group and 27.3% in the Age > 50 – ≤ 65 group had at least one episode of Grade ≥ 3 lymphopenia during the 96-week treatment period
 - In patients treated with placebo, 1.6% (9/566) in the Age ≥ 18 – ≤ 50 group and 1.3% (1/75) in the Age > 50 – ≤ 65 group had at least one episode of Grade ≥ 3 lymphopenia during the same period
- The estimated median time to improvement from Grade ≥ 3 to Grade ≤ 2 lymphopenia was 6.0 (IQR: 3.1, 12.1) weeks for patients in both age groups

Patients with Grade ≥ 3 lymphopenia





RESULTS

- In patients treated with cladribine tablets 3.5 mg/kg who had Grade ≥ 3 lymphopenia, the incidence of infection-related TEAEs was 19.71 versus 23.78 Adj-TEAE per 100 PY in the Age ≥ 18 – ≤ 50 and > 50 – ≤ 65 years groups, respectively
 - Common infection-related TEAEs were influenza, viral upper RTI, upper RTI, and herpes zoster

Common infection-related TEAEs in patients who had at least one episode of Grade ≥ 3 lymphopenia over the course of 96 weeks on study (≥ 1.0 Adj-TEAE per 100 PY in patients of either age group treated with cladribine tablets)

	Cladribine tablets 3.5 mg/kg			
	Age ≥ 18 – ≤ 50 years (N=205) ^{a,c}		Age > 50 – ≤ 65 years (N=30) ^{b,c}	
	n (%)	Adj-TEAE per 100 PY (95% CI)	n (%)	Adj-TEAE per 100 PY (95% CI)
Any infection-related TEAE	105 (51.2)	19.71 (16.28, 23.87)	17 (56.7)	23.78 (14.78, 38.25)
Influenza	31 (15.1)	3.72 (2.62, 5.29)	5 (16.7)	4.83 (2.01, 11.60)
Viral upper RTI	48 (23.4)	6.43 (4.84, 8.53)	5 (16.7)	4.73 (1.97, 11.36)
Upper RTI	28 (13.7)	3.36 (2.32, 4.86)	5 (16.7)	4.60 (1.92, 11.06)
Herpes zoster	7 (3.4)	0.76 (0.36, 1.59)	4 (13.3)	3.37 (1.27, 8.99)
Bronchitis	12 (5.9)	1.33 (0.76, 2.35)	3 (10.0)	2.68 (0.86, 8.31)
Pneumonia	2 (1.0)	0.21 (0.05, 0.86)	2 (6.7)	1.70 (0.43, 6.82)
RTI	3 (1.5)	0.32 (0.10, 0.99)	2 (6.7)	1.67 (0.42, 6.69)

^aOf the nine placebo-treated patients who had Grade ≥ 3 lymphopenia, four (44.4%) had infections: one case each of influenza, RTI, RTI viral, and viral infection; two cases of upper RTI. ^bInfection was not reported in the one placebo-treated patient who had Grade ≥ 3 lymphopenia. ^cResults should be interpreted with caution due to a large difference between sample sizes.



CONCLUSIONS

- **In both younger and older age groups, 25.2–27.3% of patients treated with cladribine tablets and 1.3–1.6% of patients treated with placebo experienced transient Grade ≥ 3 lymphopenia**
 - **The rate of certain infection-related TEAEs was numerically higher in the older versus younger patients treated with cladribine tablets**
 - **Six cases of infection-related TEAEs were reported in younger patients treated with placebo only**
- **The results presented should be interpreted with caution due to some limitations:**
 - **This is a *post hoc* analysis of data from previous Phase 3 trials that were not powered to evaluate differences between older and younger patient groups**
 - **The sample size in the older patient group was low versus the younger patient group**
 - **Adj-TEAE per 100 PY is based on exposure years. A low sample number will lead to reduced exposure time, which will impact TEAE adjustment**

Abbreviations: Adj, adjusted; AE, adverse event; DMT, disease-modifying therapy; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IQR, interquartile range; MS, multiple sclerosis; PY, patient years; RTI, respiratory tract infection; SD, standard deviation; TEAE, treatment-emergent AE

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LAY SUMMARY

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