The Sydney Cladribine Cohort: Five year data

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Background

- Cladribine is an effective treatment for MS, it has been shown to reduce the number of new lesions and decrease disability accumulation in the short and medium term. It has a large effect on the suppression of B cells however, its long-term effect on immunoglobin (IG) levels is not well described[1,2]
- Two years of therapy can give up to four years of response in many patients[4]. The issue of retreatment and timing has not been well studied. Real-world evidence can provide information about the indications, benefits and risk of further treatment.
- There are few publications that describe an additional courses of medication before of after 4 years[3]. Real world studies can inform these decisions about retreatment after four years or about the administration of additional courses within the first four years.

Methods

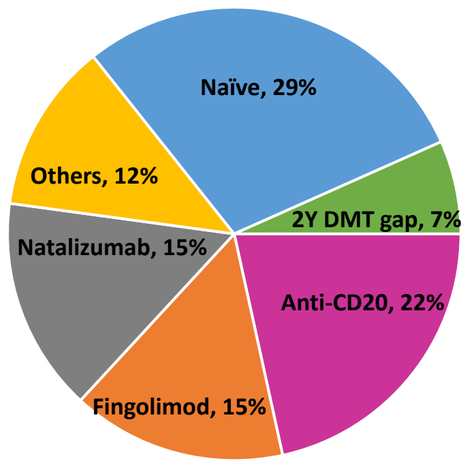
- This is an observational study with retrospective and prospective data collected from Neurology Clinic at Liverpool hospital of patients treated with cladribine from 2018 to April 2023. The following data were collected at baseline: age, gender, disease duration, name and number of prior disease modifying therapy (DMT) use, cladribine course dates, laboratory tests including immunology screening (Lymphocyte, $CD4^+$, $CD8^+$ $CD19^+$, IgG, IgM, expanded disability status scale (EDSS), magnetic resonance imaging (MRI) activities, and relapses. The data analysed were extracted from MSBase.
- Cladribine was administered as per the product label and standard international guidelines. In this cohort an additional requirement was that patients' lymphocyte count needed to be ≥ 0.7 x 10^9/L before starting the second treatment week in each year. The aim was to reduce incidence of lymphopenia and adverse events. As a result some patients had their second treatment week delayed.
- EDSS was assessed at 6-month intervals and MRI was performed annually. Laboratory tests were performed at 3 week, 1, 3, 6, and 12 month intervals in the first two years. Lesions, relapses and AES were monitored throughout the observation period.
- Patients who completed a year's course of cladribine and had more than 6-month's follow-up were included. Patients who did not complete a full one year's course of medication (1.75mg/kg), or who had limited clinical data were excluded from the analysis.

Statistical Analysis

- Annualized relapse rate was calculated using Poisson Regression in SPSS.15, relapse rate was adjusted for age. The number of cladribine courses, disease duration, number of previous DMTs, and individualized cladribine treatment length were determined.
- The overall adjusted annualized relapse rate (ARR) was 0.06 (95% CI: 0.05-0.07, *p*: <0.001).
- Analysis of time to relapse was performed using Cox regression and adjusted for duration of disease, previous DMTs, and yearly cladribine courses (1.75mg/kg). Disease duration and the number of previous DMTs were negatively associated with time to first relapse.
- Repeated measures ANOVA showed significant improvement in mean EDSS (4.04 to 3.83, *p*= 0.015) score over time. There was a significant decrease in the lymphocyte (*p*<0.001); $CD4^+$ (*p*<0.001); and $CD8^+$ (*p*<0.001) counts as well as IgM (*p*=0.014) over time. The $CD19^+$ counts and IgG levels did not significantly change.

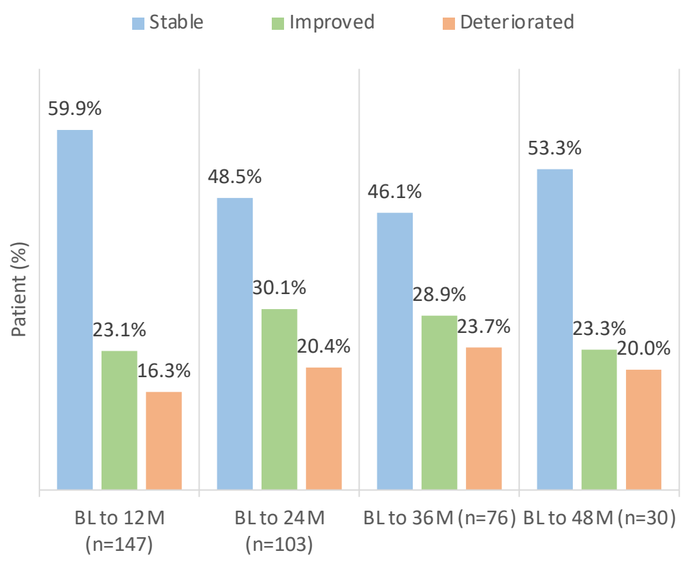
Clinical Results

Cohort previous DMT breakdown

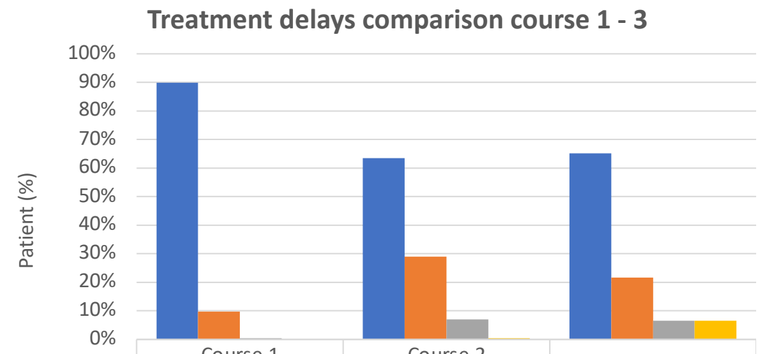


Previous DMTs (n)	Mean Age ± SD	Mean duration of disease (Y) ± SD	Sex F - M	Mean # of DMTs pre-Cladribine
Anti-CD20 (n=55)	52 ± 11	16 ± 8	44 F – 11 M	3
Fingolimod (n=39)	53 ± 12	22 ± 10	32 F – 7 M	2
Natalizumab (n=39)	52 ± 12	17 ± 9	34 F – 5 M	2
Others (n=31)	53 ± 12	15 ± 8	29 F – 2 M	2
Naïve (n=74)	44 ± 14	10 ± 9	58 F – 16 M	n/a
2-Year DMT gap (n=17)	47 ± 15	20 ± 8	12 F – 5 M	2
Total Cohort (255)	**50 ± 13**	**16 ± 10**	**209 F – 46 M**	**2.7**

EDSS change: Cladribine baseline (BL) to 48M



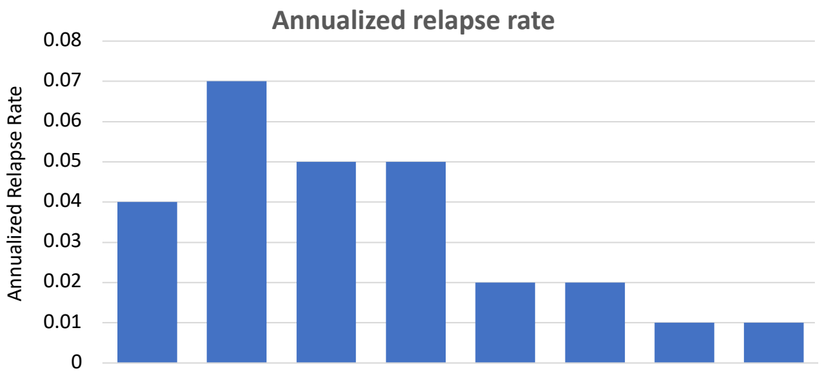
Treatment delays comparison course 1 - 3



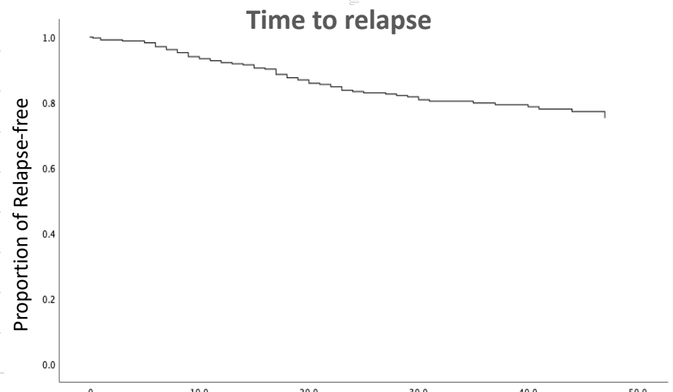
	Course 1 (n=255)	Course 2 (n=200)	Course 3 (n=46)
Full Dose	89.8%	63.5%	65.2%
Delayed W5	9.8%	29.0%	21.7%
Withheld W5	0.4%	7.0%	6.5%
Switched DMT	0.0%	0.5%	6.5%

W5 Delay comparison	Course 1 (n=25)	Course 2 (n=58)	Course 3 (n=10)
Average W5 delay (Days)	94	95.2	110.7

Annualized relapse rate



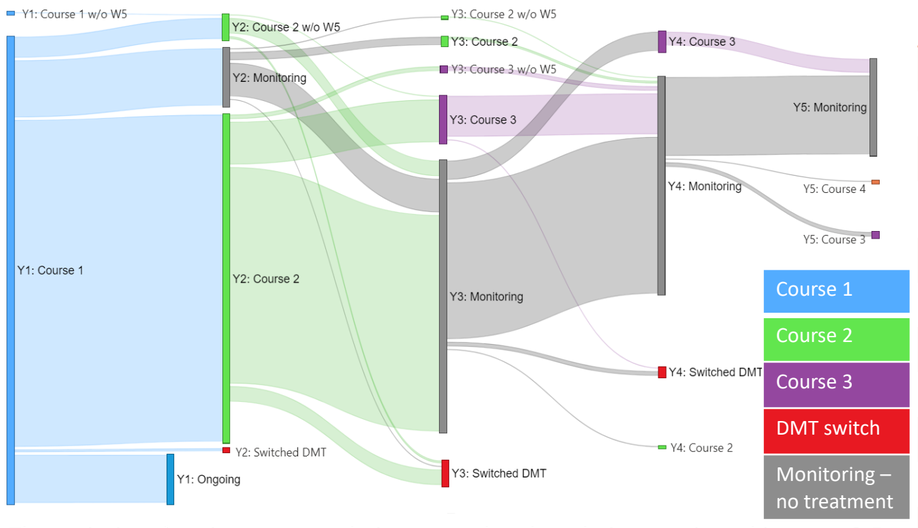
Time to relapse



No. at Risk	255	247	228	222	211	180	148	111
No. Relapses	9	17	13	13	6	4	2	3
95% CI	0.02-0.07	0.04-0.11	0.03-0.09	0.03-0.09	0.01-0.05	0.006-0.04	0.002-0.03	0.004-0.04

Variable Test	Coefficient	p-value	HR
Duration of Disease	-0.040	0.017	0.961
No. Previous DMTs	0.158	0.018	1.171
No. Cladribine Courses	0.817	<0.001	2.264

Retreatments over 5 years

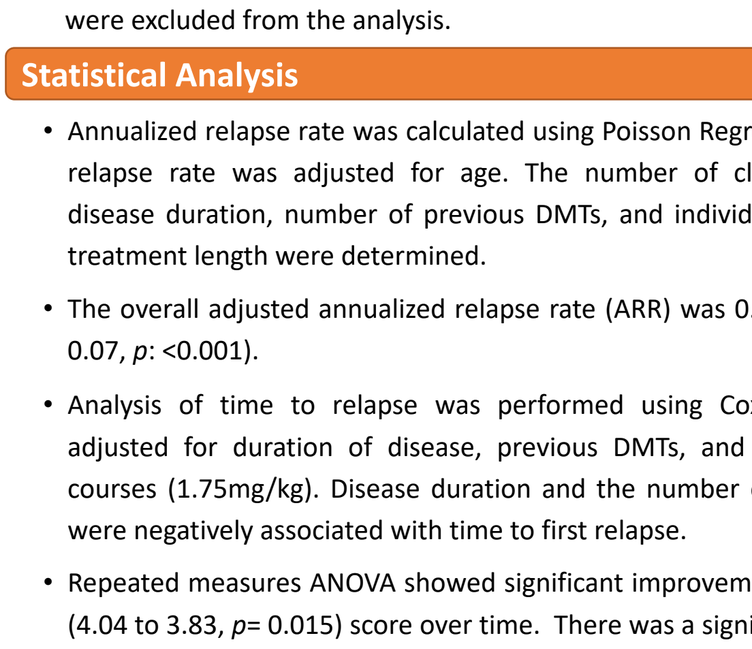


The majority of patients are not being treated and are being monitored in years 3-5. A small number of patients started their second course in third year due to delays. There are some people being retreated with a third course, some in year 3 and others in year 4. There is a small number of people that have changed to other DMTs.

AEs (Total n)	Course 1 (n=255)	Course 2 (n=200)	Course 3 (n=46)
Hair loss (8)	6	2	
Shingles (11)	8	2	1
Cold sores (6)	3	3	
Upper Respiratory Infection (7)	5	1	1
Other infections (5)	3	2	
Other cancers (2)	1		1
Mucositis (6)	5	1	
Digestive tract issues (8)	5	3	
Appendicitis (1)	1		
UTI (11)	3	7	
Skin issues (2)	1		1
Heart Issues (1)	1		
Other issues (8)	6	2	

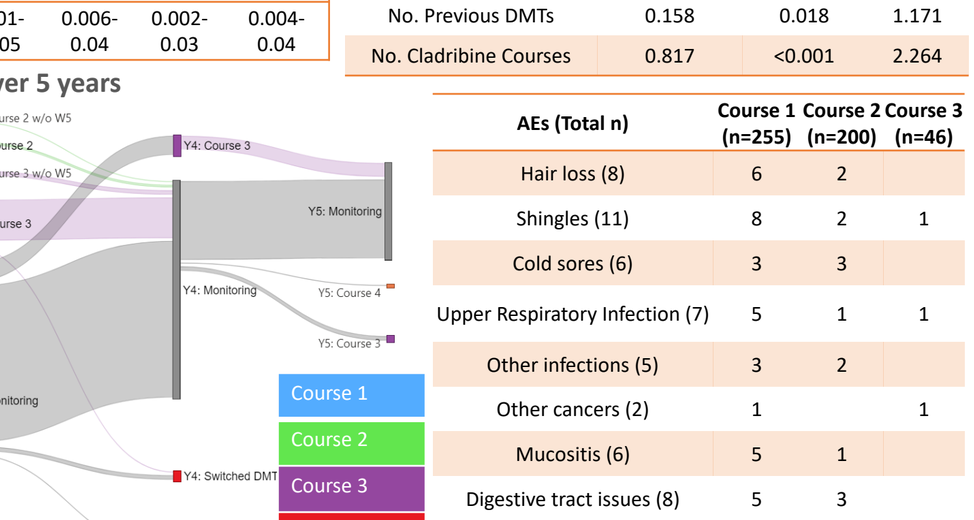
Laboratory Results

$CD4^+$, $CD8^+$, $CD19^+$ Baseline course 1 and 2 to 36M

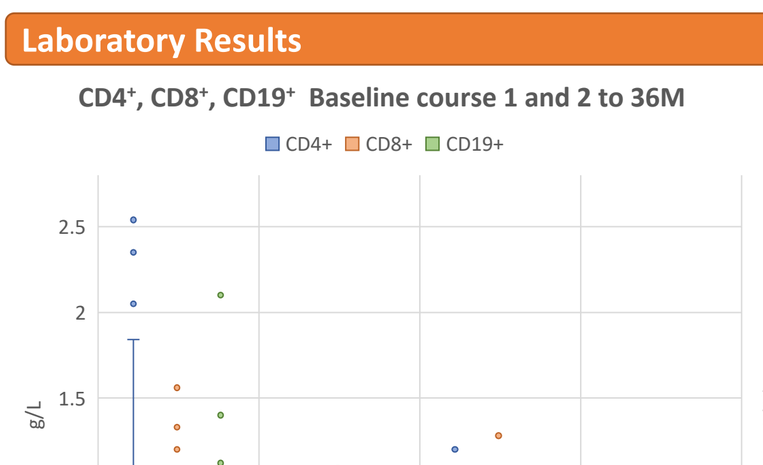


Max lymphopenia grade reached during Course 1-3

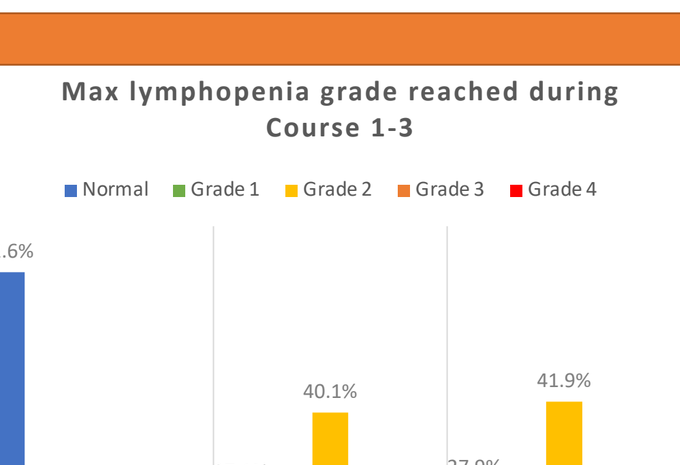
Mean lymphocyte count over 48 months



IgG – Baseline course 1 to 48M



IgM – Baseline course 1 to 48M



Cohort IgG	Mean ± SD	Min	Q1	Q2	Q3	Max
Course 1 BL (n=146)	9.73 ± 2.93	3.82	7.48	9.92	11.20	19.70
Course 2 BL (n=134)	10.03 ± 2.47	3.64	8.42	10.24	11.52	16.80
Course 3 BL (n=33)	9.13 ± 2.00	6.12	7.22	9.28	10.38	13.37

Cohort IgM	Mean ± SD	Min	Q1	Q2	Q3	Max
Course 1 BL (n=139)	0.85 ± 0.58	0.10	0.46	0.66	1.09	3.83
Course 2 BL (n=127)	0.85 ± 0.49	0.27	0.50	0.76	1.05	3.24
Course 3 BL (n=33)	0.67 ± 0.39	0.20	0.46	0.58	0.85	2.26

Conclusion

- This population was relatively older (>50yrs) and had a higher average number of DMTs (2.7) prior to starting cladribine compared with most other studied populations.
- The frequency of side effects was low. Ensuring the lymphocyte count was greater than ≥ 0.7 x 10^9/L before second treatment week may reduce risks. Despite patients receiving multiple DMTs, the rate of Grade 4 Lymphopenia was very low and there were few side effects and well tolerated.
- Annualised relapse rate was low which may relate to the age and number of previous DMTs in the cohort.
- The EDSS of around 80% of patients remained stable or improved at 48 month.
- Cladribine had no effect on IgG levels over 4 years, this maybe a consideration in choice of DMT.

Limitations

- Observational study.
- COVID pandemic meant some EDSS assessments and blood test were missed or fell outside of their specific timepoints. Some EDSS were performed over the phone due to lockdowns.

Disclosures & References

1. Oreja-Guevara, C. *et al.* (2023a) 'Expert opinion on the long-term use of cladribine tablets for multiple sclerosis: Systematic Literature Review of real-world evidence', *Multiple Sclerosis and Related Disorders*, 69, p. 104459. doi:10.1016/j.msard.2022.104459.
2. Sorensen, P.S. *et al.* (2023) 'Real-world experience of cladribine treatment in relapsing-remitting multiple sclerosis: A Danish nationwide study', *Multiple Sclerosis and Related Disorders*, 70, p. 104491. doi:10.1016/j.msard.2022.104491.
3. Santos, Mónica *et al.* (2023) 'Safety and effectiveness of cladribine in multiple sclerosis: Real-world clinical experience from 5 tertiary hospitals in Portugal', *Clinical Neuropharmacology*, 46(3), pp. 105–111. doi:10.1097/wnf.0000000000000552.
4. Giovannoni G et al. (2018) 'Safety and efficacy of Cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study'. *Mult Scler.* Oct;24(12):1594-1604. doi: 10.1177/1352458517727603.

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