Variation in cladribine-induced lymphocyte depletion

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Background

- Cladribine (2-chloro-deoxyadenosine) is a purine nucleoside analogue approved for use in active relapsing Multiple Sclerosis
- Cladribine a prodrug that is metabolised into toxic metabolites via a rate-limiting phosphorylation step catalysed by deoxycytidine kinase (dCK), and reversed by 5-nucleotidases 5NTCI and 5NTCII [1,2]
- Lymphocytes express high levels of dCK, rendering them especially vulnerable to cladribine-mediated cytotoxicity
- Cladribine induces depletion of lymphocytes followed by slow repopulation over a time course of months [3]
- Analysis of lymphocyte subsets in trial populations have suggested that there is substantial inter-individual variability in the magnitude and time course of lymphocyte depletion following cladribine treatment [4]

Objective

- We aimed to characterise inter-individual variability in a real-world cohort treated with either oral cladribine or off-label subcutaneous cladribine, and trial populations

Methods

- Absolute lymphocyte counts (ALC) were measured pre and post treatment in people with MS (pwMS) who received oral cladribine for highly active relapsing MS between January 2018 and July 2019 at the Royal London Hospital (RLH)
- Previously published data on absolute lymphocyte counts pre and post cladribine treatment were taken from the following groups:
  - subset of individuals in the CLARITY trial with longitudinal lymphocyte data [5]
  - pwMS who received off-label subcutaneous cladribine at the Royal London Hospital [6]
- Individuals receiving oral cladribine at the Royal London Hospital had a dose of 3.5mg/kg and those receiving subcutaneous cladribine had 30-40mg initially based on weight and 0-30mg four weeks later depending on ALC
- Individual lymphocyte count nadirs were compared between treatment groups using the Kruskal–Wallis test, a *P*-value of <0.05 was taken as significant. Pairwise comparisons were done using the Wilcoxon rank-sum test and a *P*-value of <0.0083 taken as significant according to a Bonferroni correction
- This service evaluation was registered with the Barts Health Clinical Effectiveness Unit (registration number: 10596)

Results

- Median ALC nadir was reached at week 8, week 12, week 9 and week 16 in the subcutaneous, oral, CLARITY 3.5 and CLARITY 5.25 groups respectively (Fig 2) during year 1
- There was a significant difference between the lymphocyte count nadirs ($P < 0.001$) in year 1 between all treatment groups
- There was no significant difference between the lymphocyte count nadirs in the subcutaneous , RLH oral and CLARITY 3.5 groups (Table 3) in year 1 of treatment

Table 1: Characteristics of individuals in each treatment group

	RLH Oral n = 37	S/c n = 211	CLARITY 3.5 n = 103	CLARITY 5.25 n = 105
Mean age	33	44	38	41
Gender				
-Male	8	79	32	30
-Female	29 (78%)	132 (63%)	71 (69%)	75 (71%)
Median EDSS	2.0	4.8	3.0	3.5

RLH Oral: Oral cladribine 3.5mg/kg **S/c:** Subcutaneous cladribine **CLARITY 3.5:** CLARITY 3.5mg/kg group **CLARITY 5.25:** CLARITY 5.25mg/kg group **EDSS**: Expanded Disability Status Scale.

Table 2: Most severe grade of lymphopenia reached 12 months after first course of treatment

Grade of lymphopenia	Number of patients (%)			
	RLH Oral	S/c	CLARITY 3.5	CLARITY 5.25
Grade 1	12 (32%)	49 (24%)	21 (20.4%)	13 (12.4%)
Grade 2	6 (16%)	75 (37%)	36 (35.0%)	50 (47.6%)
Grade 3	5 (14%)	9 (4%)	16 (15.5%)	34 (32.4%)
Grade 4	0 (0%)	0 (0%)	0 (0%)	3 (2.9%)

RLH Oral: Oral cladribine 3.5mg/kg **S/c:** Subcutaneous cladribine **CLARITY 3.5:** CLARITY 3.5mg/kg group **CLARITY 5.25:** CLARITY 5.25mg/kg group. Grade of lymphopenia as per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. **Grade 1:** <Lower normal limit - 0.8 x 10e9/L **Grade 2:** <0.8 - 0.5 x 10e9 /L **Grade 3:** <0.5 - 0.2 x 10e9 /L **Grade 4:** <0.2 x 10e9 /L.

Table 3: Pairwise comparisons of lymphocyte nadirs

Treatment group	S/c	RLH oral	CLARITY 3.5
RLH oral	0.564	-	-
CLARITY 3.5	0.029	0.077	-
CLARITY 5.25	**<0.001**	**<0.001**	**<0.001**

Pairwise comparisons of individual lymphocyte nadirs during the first course of therapy by treatment group using Wilcoxon rank-sum test. Bonferroni correction applied for multiple testing. *P*-value <0.0083 taken as significant.

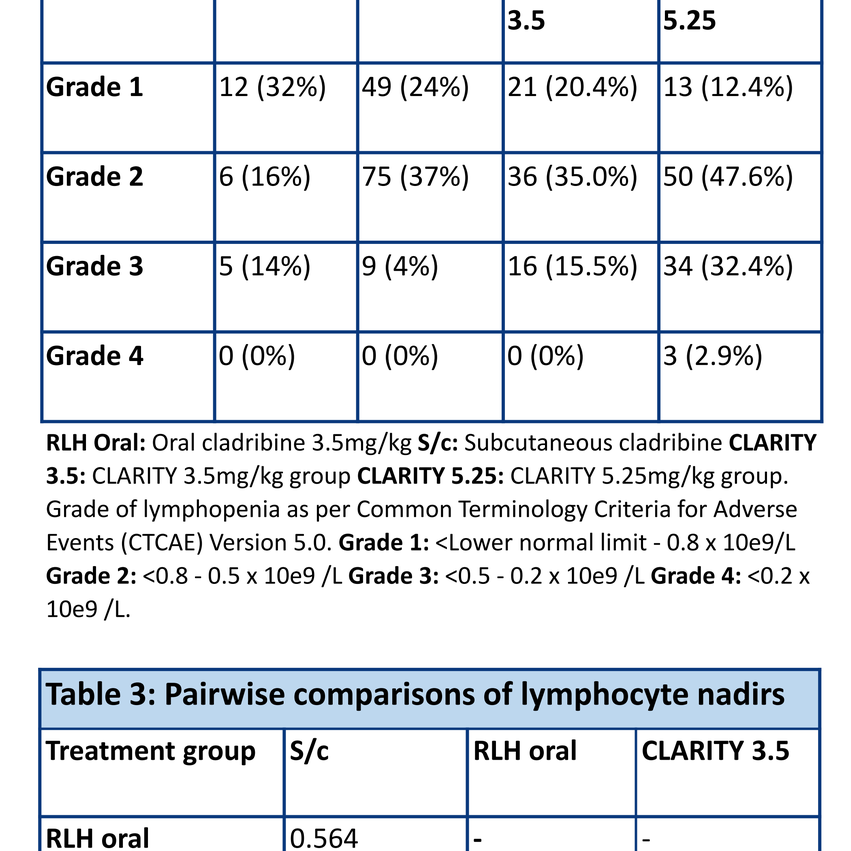

Fig. 1 Boxplot showing percentage change of absolute lymphocyte count from baseline between weeks 8 and 13.

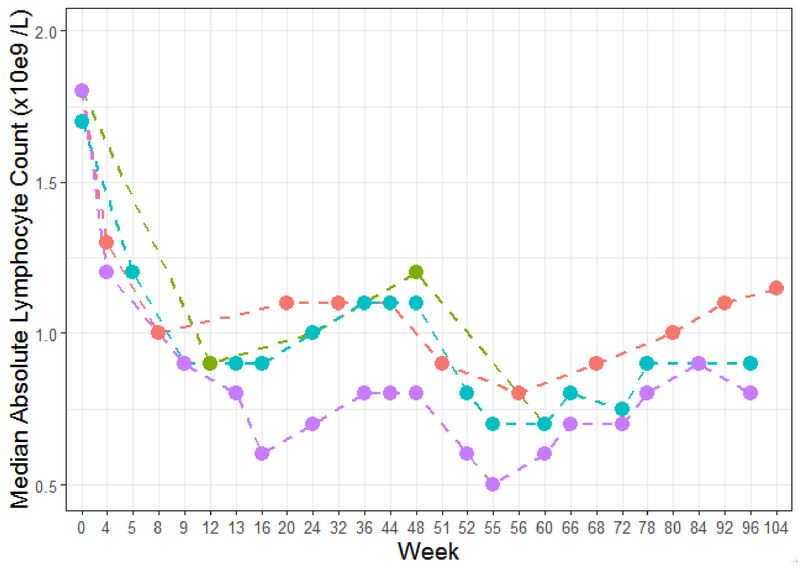

Fig. 2 Median absolute lymphocyte count over time. ● RLH Oral cladribine 3.5mg/kg, ● Subcutaneous cladribine, ● CLARITY 3.5mg/kg group, ● CLARITY 5.25mg/kg.

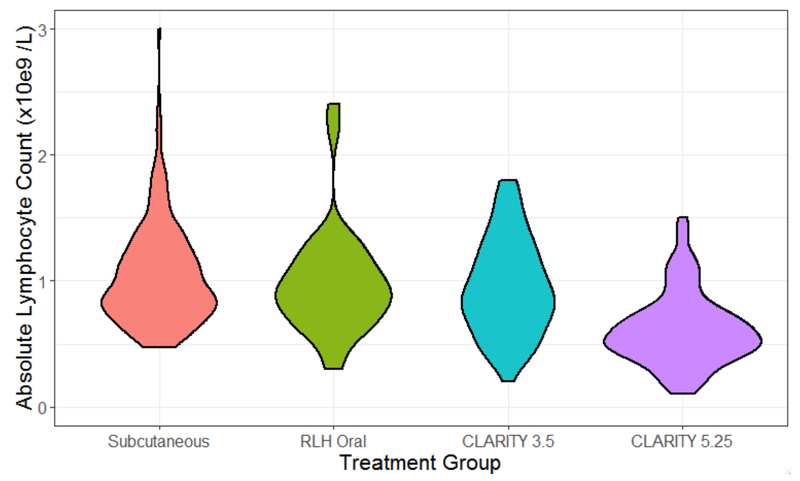

Fig. 3 Distribution of absolute lymphocyte count at time point of median absolute lymphocyte count nadir. One individual in Subcutaneous group removed from graph.

Conclusions

- The 5.25mg/kg CLARITY trial cohort nadir was reached later than the 3.5mg/kg CLARITY trial cohort and was significantly lower than the nadir of the other groups
- The 3.5mg/kg CLARITY trial cohort was comparable with the RLH oral and subcutaneous cohort in terms of ALC nadir
- Severe lymphopenia was rare in the trial and real-world cohort and some individuals were noted to have only mild lymphocyte reduction
- There is large variability in lymphocyte depletion among pwMS following cladribine administration
- Understanding the factors that explain this inter-individual variability is an important step towards personalised treatment

What this adds

- Magnitude and kinetics of lymphocyte depletion did not differ substantially between the subcutaneous cladribine regime and bioequivalent oral regimes

References

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Disclosures

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