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Clinical impact of Ocrelizumab dosing delays and their association with CD-19⁺ B-cell repletion during the COVID-19 pandemic

Introduction

The COVID-19 pandemic significantly impacted the healthcare of many people with multiple sclerosis (pwMS). Many PwMS experienced interruptions to their care with cancelled appointments, investigations or even delays to disease modifying therapy (DMT), with altered dosing regimen of ocrelizumab most common.[1]

At the start of the pandemic the Association of British Neurologists[2] recommended considering delaying re-treatment cycles of ocrelizumab during periods of high infection. This was compounded by the suggestion that anti-CD20 therapies may increase the likelihood of hospitalisation with COVID-19 and need for intensive care,[3] although this has not been reflected in data from clinical trials and post-marketing pharmacovigilance.[4] Evidence of persistent disease suppression long after stopping Rituximab[5] suggested extended dosing intervals may be safe with ocrelizumab given their similar effects on long-term B-cell depletion. CD19⁺ B-cell repletion to 1% of lymphocyte population was suggested[2] as a possible marker to individualise dosing interval extension[6].

Objectives

- To identify whether delays of Ocrelizumab infusion beyond 6months impacted on clinical relapses or radiological activity in pwMS.
- To explore how CD19⁺% population reflected dosing delay, relapses and radiological activity

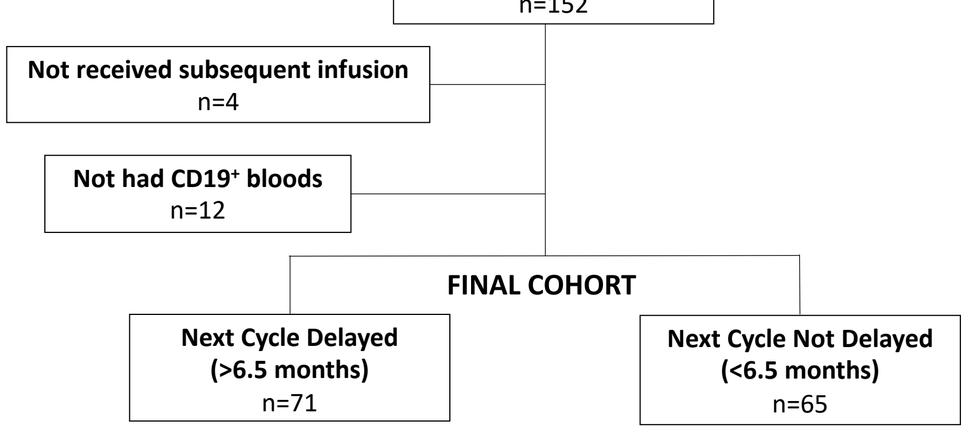
Methods

From 15th July 2020, all pwMS attending Royal Stoke University Hospital for Ocrelizumab infusions had blood sampling for TBNK lymphocyte subsets (T cells (CD3⁺), B cells (CD19⁺) and NK cells (CD16/56⁺)

We retrospectively reviewed the electronic database of pwMS on Ocrelizumab and identified all patients who had delays in treatment during the COVID-19 pandemic. Patients were included if they had taken at least 1 full initial dose (two 300mg infusions 14 days apart) of Ocrelizumab, received by a subsequent 600mg infusion during the observation period and also had TBNK lymphocyte blood sampling to obtain CD19⁺ levels. A cut-off for delay in treatment was set at 200 days prior to last dose (~6.5 months)

Baseline clinical data was extracted from electronic clinical records (see results table). Clinical notes and letters were reviewed for documented clinical relapses and any MRI scan reports following the date of previous ocrelizumab infusion were reviewed for evidence of radiological activity (gadolinium-enhancing lesions or new or enlarging T2 lesions).

Figure 1: Flowchart of the Study



Discussion

An average 5-month delay of subsequent ocrelizumab cycle did not adversely impact on clinical relapses or radiological activity over the subsequent 4.5 months, despite significant CD19⁺ repletion and even though most of our patients had received only 1 or 2 previous treatment cycles.

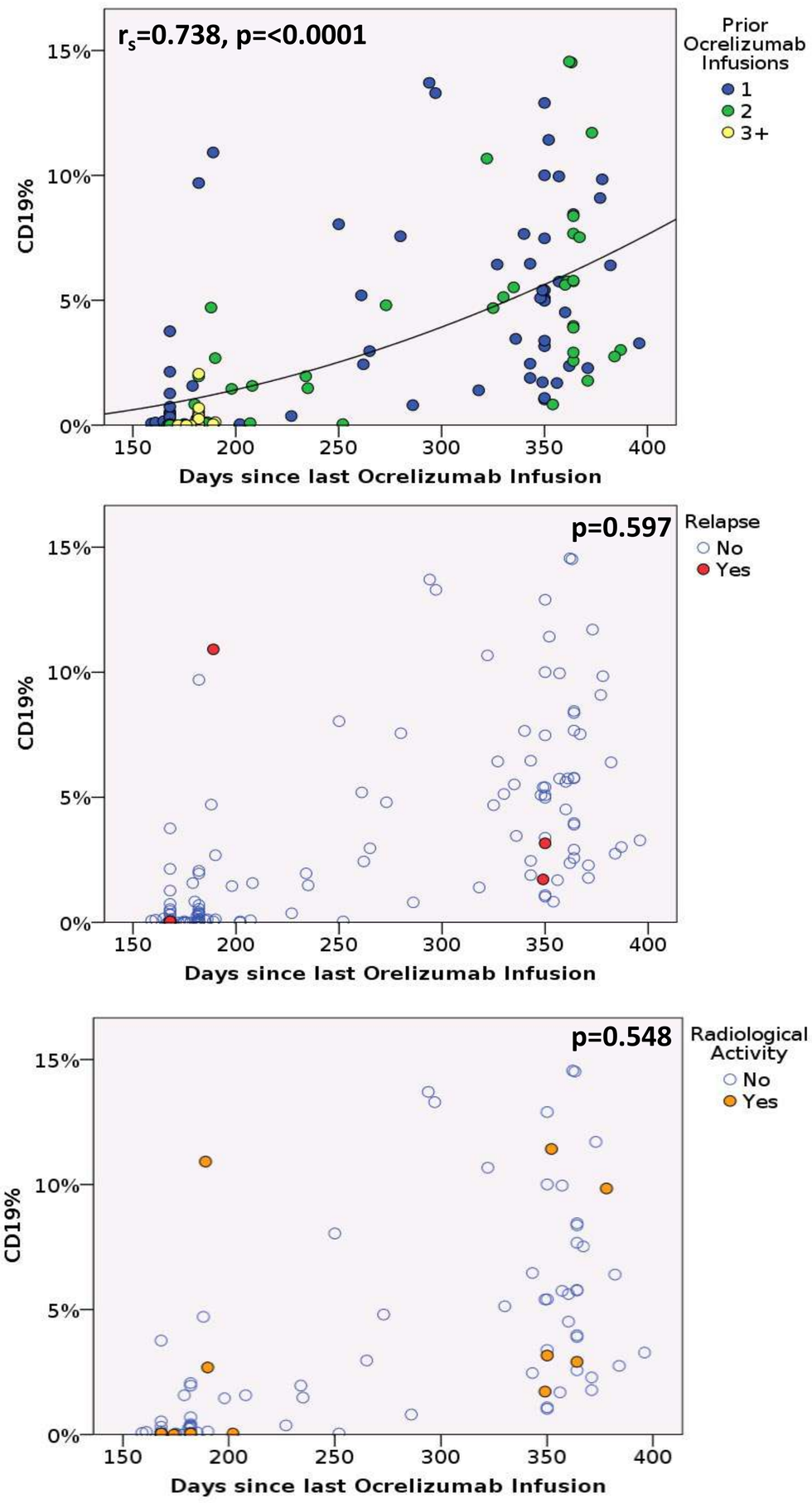
Our results are consistent with the ocrelizumab phase II extension trial, where annualised relapse rates and 6-month disability progression remained low during a 12–18-month treatment free period after 3-4 treatment cycles. The small number of patients imaged had no radiological activity and much fewer adverse effects and infections were reported.[7]

In the phase II extension trial, the median time for CD19⁺ B-cells to return to baseline levels or lower limit of normal was 15 months. Although, we did not have baseline CD19⁺ levels after an average of 11 months 90% of patients had repopulated to 1%. However, these are likely immature and immune naïve B-cells from the bone marrow.[8] Early CD19⁺ repletion does not directly reflect disease activity and may herald a safe window to extend dosing, although the duration of the window remains unclear and may display high inter- and intra-individual variation.[9] This may require significant monitoring burden but would reduce potential side effects, infusion visits and associated costs.

Conclusions

Our real-world observations suggest a single delayed or even missed cycle of ocrelizumab is unlikely to impact on disease activity in the short-term. A direct head-to-head study of extended dosing ocrelizumab versus standard dosing interval is warranted to assess long-term efficacy, safety and cost-effectiveness.

Figure 2: Associations with CD19⁺%



Results

		Delayed	Not Delayed	p-value
Demographics		n=71	n=65	
Age		46.3 ± 10.0	42.8 ± 14.0	0.140
Disease Duration		9.9 ± 7.4	9.5 ± 6.9	0.865
Female, n (%)		58 (82%)	47 (72%)	0.193
EDSS		3.4 ± 1.5	3.2 ± 1.7	0.408
RRMS, n (%)		64 (94%)	55 (90%)	0.519
PPMS, n (%)		4 (6%)	6 (10%)	
Previous DMTs, n (%)	0	34 (48%)	31 (48%)	0.547
	1	22 (31%)	15 (23%)	
	2	10 (14%)	13 (20%)	
	3	4 (6%)	5 (8%)	
	4	0	1 (2%)	
First Line Injectables		22	23	0.586
First line Orals		9	11	0.485
Fingolimod		2	6	
Alemtuzumab		1	0	
Natalizumab		18	13	
Prior infusions n (%)	1	43 (61%)	30 (46%)	<0.001*
	2	28 (39%)	22 (34%)	
	3+	0	13 (20%)	
Results				
Days since last cycle		330.2 ± 50.4	176.3 ± 8.4	
Days observed post next cycle		137.9 ± 42.5	142.0 ± 83.0	
CD19⁺ %		5.22 ± 3.79	0.77 ± 1.93	<0.001*
CD19⁺ level >1%, n (%)		64 (90%)	11 (17%)	<0.001*
Clinical Relapse		3/71 (4.2%)	2/65 (3.1%)	0.670
Radiological Activity		6/50 (12%)	6/39 (15%)	0.758
New/enlarging lesions		6	6	
Enhancement		0	3	

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