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Original article

CD19 B cell repopulation after ocrelizumab, alemtuzumab and cladribine: Implications for SARS-CoV-2 vaccinations in multiple sclerosis

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ABSTRACT

Background: Ocrelizumab maintains B-cell depletion via six-monthly dosing. Whilst this controls relapsing multiple sclerosis, it also inhibits seroconversion following SARS-CoV-2 vaccination unlike that seen following alemtuzumab and cladribine treatment. Emerging reports suggest that 1–3% B-cell repopulation facilitates seroconversion after CD20-depletion.

Objective: To determine the frequency of B-cell repopulation levels during and after ocrelizumab treatment.

Methods: Relapse data, lymphocyte and CD19 B-cell numbers were obtained following requests to clinical trial data-repositories. Information was extracted from the phase II ocrelizumab extension (NCT00676715) trial and the phase III cladribine tablet (NCT00213135) and alemtuzumab (NCT00530348/NCT00548405) trials obtained clinical trial data requests

Results: Only 3–5% of people with MS exhibit 1% B-cells at 6 months after the last infusion following 3–4 cycles of ocrelizumab, compared to 50–55% at 9 months, and 85–90% at 12 months. During this time relapses occurred at consistent disease-breakthrough rates compared to people during standard therapy. In contrast most people (90–100%) exhibited more than 1% B-cells during treatment with either cladribine or alemtuzumab.

Conclusions: Most people demonstrate B cell repletion within 3 months of the last treatment of alemtuzumab and cladribine. However, few people repopulate peripheral B-cells with standard ocrelizumab dosing. Controlled studies are warranted to examine a view that delaying the dosing interval by 3–6 months may allow more people to potentially seroconvert after vaccination.

1. Background

Therapeutic B cell targeting antibodies such as ocrelizumab and rituximab are used as a maintenance treatment for the control of multiple sclerosis (MS). Their efficacy may relate to either the direct long-term depletion of memory B cells and development of regulatory B cells within the regenerating CD19 population (Baker et al., 2020a) or indirectly through the blockade of T cell activity (Jelcic et al., 2018). Six-monthly dosing schedules, as used in MS, maintain continuous CD20+ B cell suppression in the periphery.

Given the blunted antibody response to other vaccines (Baker et al., 2020b) it is not surprising that CD20-depleting antibodies, notably rituximab and ocrelizumab, repeatedly and consistently appear to induce poor seroconversion following natural infection with SARS-CoV-2 (Louapre et al., 2020; Sormani et al., 2021a). Furthermore seroconversion in CD20-depleted, COVID-19 vaccinated individuals is universally

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Table 1
CD19 B cell repletion and relapse rates after repeated ocrelizumab infusions.

Treatment	Time from Treatment Onset	Number of CD19+ cells of total lymphocytes/total 1% B cells	2% B cells	3% B cells
Ocrelizumab 3 cycles	6 months	4/81 (5%)	3/81 (4%)	2/81 (2%)
	9 months	43/80 (54%)	30/80 (38%)	22/80 (28%)
Ocrelizumab 4 cycles	12 months	76/84 (90%)	68/84 (81%)	57/84 (68%)
	15 months	44/48 (92%)	41/48 (85%)	35/48 (73%)
	18 months	29/31 (93%)	25/31 (81%)	22/31 (71%)
	6 months	1/39 (3%)	1/39 (3%)	1/39 (3%)
	9 months	20/40 (50%)	11/40 (28%)	8/40 (20%)
	12 months	35/41 (85%)	25/41 (61%)	19/41 (46%)
	15 months	26/28 (93%)	20/28 (71%)	14/28 (50%)
	18 months	26/28 (93%)	22/28 (79%)	20/28 (71%)

Treatment	Time from Treatment	Number of PwMS with the indicated number of CD19+ B cells > 1 cell/μl	>5 cells/μl	>10cells/μl	>20 cells/μl	>30 cells/μl
Ocrelizumab 3 cycles	0 months	68/92 (74%)	25/92 (27%)	13/92 (14%)	8/92 (9%)	8/92 (9%)
	6 months	67/84 (80%)	20/84 (24%)	6/84 (7%)	4/84 (5%)	4/84 (5%)
Ocrelizumab 4 cycles	9 months	77/83 (93%)	64/83 (77%)	51/83 (61%)	41/83 (49%)	30/83 (36%)
	12 months	84/84 (100%)	81/84 (96%)	76/84 (90%)	75/84 (89%)	70/84 (83%)
	15 months	49/49 (100%)	47/49 (96%)	46/49 (94%)	46/49 (94%)	42/49 (85%)
	18 months	37/37 (100%)	36/37 (97%)	34/37 (92%)	31/37 (84%)	30/37 (81%)
	0 months	36/46 (78%)	13/46 (28%)	5/46 (11%)	0/46 (0%)	0/46 (0%)
	6 months	31/39 (79%)	7/39 (18%)	1/39 (3%)	1/39 (3%)	1/39 (3%)
	9 months	42/43 (98%)	34/43 (79%)	24/43 (56%)	19/43 (44%)	13/43 (30%)
	12 months	41/41 (100%)	39/41 (95%)	38/41 (93%)	31/41 (76%)	24/41 (59%)
	15 months	29/29 (100%)	29/29 (100%)	28/29 (97%)	25/29 (86%)	22/29 (76%)
	18 months	28/28 (100%)	28/28 (100%)	28/28 (100%)	26/28 (93%)	24/28 (86%)

Treatment	Time from Last Infusion	No.Relapse/Total	Relapse rate/yr.
Ocrelizumab 3 cycles	0–6 months	9/99	0.18
	6–9 months	4/85	0.19
	9–12 months	5/72	0.28
	12–15 months	3/77	0.16
	15–18 months	0/80	0.00
	Time from Last Infusion	No.Relapse/Total	Relapse rate/yr.
Ocrelizumab 4 cycles	0–6 months	6/49	0.24
	6–9 months	3/43	0.28
	9–12 months	1/33	0.12
	12–15 months	1/38	0.11
	15–18 months	5/42	0.48

Individuals received 600 mg ocrelizumab Q24W for 3 or 4 cycles followed an 18 month treatment-free period. The data was extracted from the phase II ocrelizumab extension study (Baker et al., 2020a) supplied, via the www.vivli.org portal, using R software. The last ocrelizumab infusion occurred around 72 weeks. Data capture was scheduled for weeks 96 (6 months), 108 (9 months), 120 (12months), 132 (15 months) and 144 (18 months). The results represent the approximate time from the last infusion (months) and report the frequency of people reaching 1%, 2% or 3% CD19 of total lymphocyte count or the absolute number of cells/μl following either 4 infusion cycles (0–72 weeks) of ocrelizumab or 3 ocrelizumab infusion cycles (24–72 weeks) after either placebo or beta interferon (0–24 weeks). At 24 weeks after last infusion 4/123 pwMS had over 40cells/μl. Relapses were ascribed to approximate times following the last infusion and the unadjusted, annualized relapse rate were calculated. PwMS people with multiple sclerosis.

poor (Achiron et al., 2021; Sormani et al., 2021b; Tallantyre et al., 2021). In contrast many people treated with cladribine tablets and alemtuzumab after therapy show seroconversion following COVID-19 vaccination (Achiron et al., 2021; Sormani et al., 2021b; Tallantyre et al., 2021).

Whilst protection from MS may result from depletion of memory B cells (Baker et al., 2017a), seroconversion has been attributed to immature/naïve B cell repletion and occurs following the development of 1–3% B cell repopulation (Madelon et al., 2021; Mrak et al., 2021; Stefanski et al., 2021; Disanto et al., 2021). However, the frequency of people achieving 1% B cell repletion at specific time intervals following ocrelizumab dosing is largely unknown (Gibiansky et al., 2021). We hypothesised that it may require an extended-dose interval to achieve 1% peripheral B cell repopulation in at least 50%, given the median time of 60–72 weeks for B cells to recover to the lower limit of normal (80 cells/μl) following ocrelizumab infusion (Baker et al., 2020a).

2. Methods

Anonymised trial data was provided by the trial sponsors following an independent panel review of the data analysis plans at clinincaltrialsdatarequest.com of the data analysis plans (#5836. #11529). The trials were performed in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided written informed consent. This analysis was not subject to further ethical review.

Access to the Roche/Genentech phase II ocrelizumab extension trial in (NCT00676715) was requested (#5984) and supplied under contract by the Vivli, Inc managed portal. Data from people with relapsing MS who had received three or four 6-monthly cycles of 600 mg ocrelizumab prior to an 18 month treatment-free observation period were used. Lymphocyte and CD19+ numbers were collected during the 18 month treatment-free follow up period (Baker et al., 2020a). Trial data were interrogated using R software. A mixed effects logistic regression was fitted with a binary marker for CD19 count above 1% of total lymphocyte count as outcome. Repeated measures for each individual were included from last treatment to 18 months post-treatment. Included as covariates were: baseline body mass Index (BMI); time in years; quadratic term for time; arm of trial.

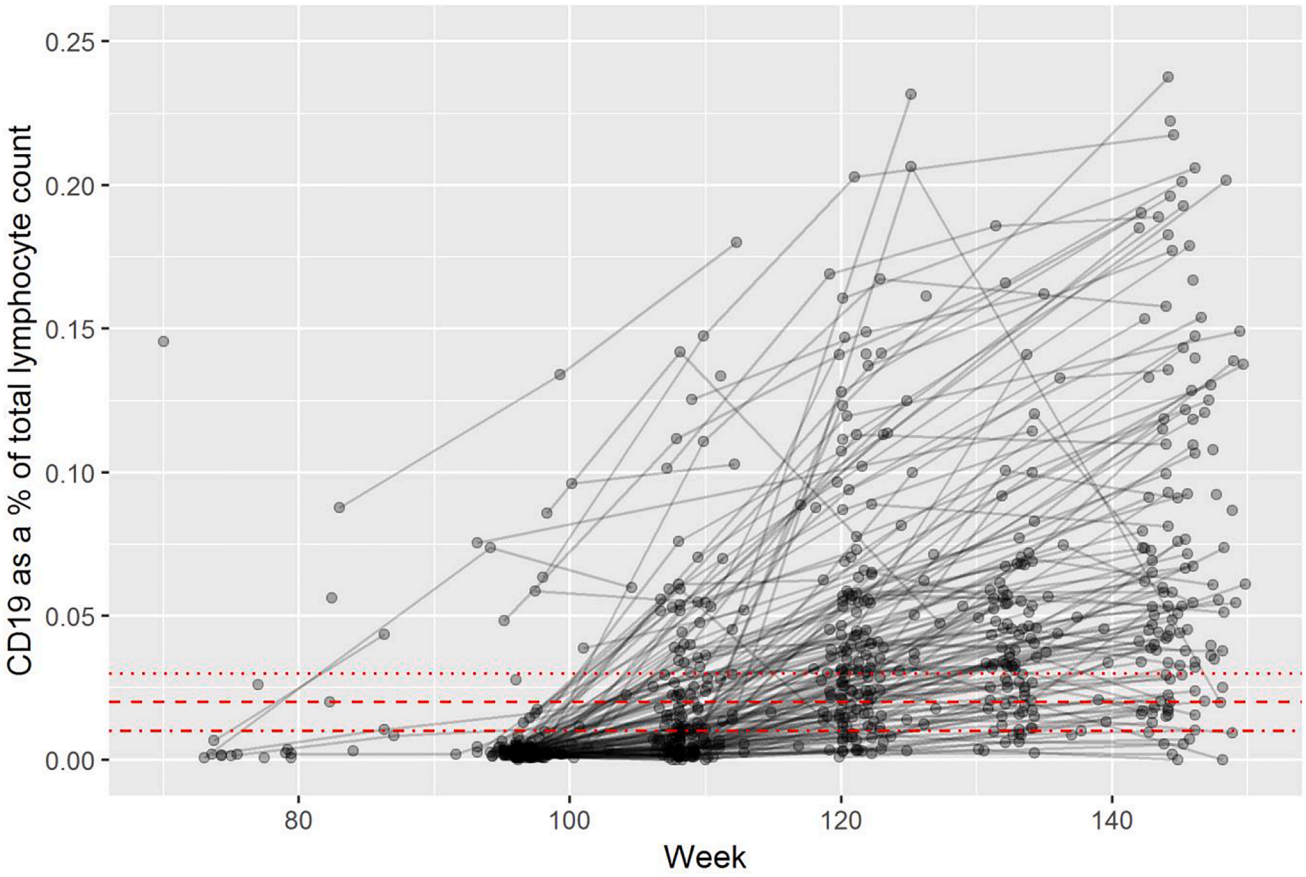

Fig. 1. Individual blood levels of B cells following ocrelizumab treatment.
People with relapsing MS were treated with 600 mg ocrelizumab from week 0–72 or 24–72. The data was extracted from the phase II ocrelizumab extension study (Baker et al., 2020a) supplied via the Vivli Inc platform using R software. The results represent the percentage CD19 count compared to total lymphocyte count repopulation over time. The 1% (dash dot), 2% (dash) and 3% (dot) CD19 B cell levels are indicated.

Lymphocyte numbers and CD19 peripheral counts information from the phase III (CLARITY) clinical trial of oral cladribine (NCT00213135) was supplied by the European Medicines Agency following a Freedom of Information request (Baker et al., 2017a). Data relating to the 3.5 mg/kg licenced dose was extracted. In addition, access to the Sanofi/Genzyme phase III alemtuzumab CARE-MS1 (NCT00530348) and CARE-MS-2 (NCT00548405) trials (Baker et al., 2017b) was requested (#11529) and supplied under contract by the clinicalstudydatarequest.com portal. Lymphocyte and peripheral blood CD19 B cell data, relating to the 12 mg licenced dose, were extracted from the CARE-MS trials.

3. Results

3–5% of people had repopulated to 1–3% B cell count by the end of the standard ocrelizumab dose interval of 6 months (Table 1). At 9 months following treatment cessation there was 50–55% B cell repopulation, and at 12 months 85–90% B cells had repopulated to at least 1% B cells (Table 1, Fig. 1). During the treatment-free observation period between week 96 to week 108 there were 9 relapses (3 cycles) and 4 relapses in people who received 4 cycles of treatment (Table 1). This frequency of disease breakthrough was comparable to 9/99 people relapsing (3 cycles) and 6/49 (4 cycles) during week 72–96 period on-standard treatment schedule (Table 1, Supplementary Figure 1 & 2). There was again evidence that baseline BMI was associated with CD19 re-population. For each increase in BMI of 5 units, the odds of having CD19 count above 1% of total lymphocyte count increased by 2.50 (95% confidence interval: 1.45–5.20; $p = 0.003$) as suggested previously (Kletzl et al., 2019; Signoriello et al., 2020).

In contrast to the persistent B cell depletion following ocrelizumab treatment (Table 1), the majority of people treated with either cladribine tablets (Table 2) or alemtuzumab (Table 3) maintained 1% B cell levels and also developed at least 10–20 CD19 B cells/μl, in contrast to levels detected after ocrelizumab (Table 1–3). B cell depletion was most marked about after the second set of treatments during the cladribine treatment cycle (Table 2). Depletion was evident within the first month of alemtuzumab treatment followed by rapid B cell repopulation (Table 3)

4. Discussion

During the COVID-19 pandemic ocrelizumab infusions were delayed by 1–3 months, with no apparent major rebound in disease activity, suggesting the potential safety of an delayed-dosing scheme (Maarouf et al., 2020; Rolfes et al., 2021; van Lierop et al., 2021; Baker et al., 2021). The importance of mounting a sterilising response relates not only to clinical severity of infection, but also that immunosuppressed individuals may harbour prolonged SARS-CoV-2 infection allowing serial mutations to develop, impacting on infectivity and immune escape (Khoury et al., 2021; Corey et al., 2021).

Given the importance of neutralizing antibody responses (Khoury et al., 2021), and the finding that protective SARS-CoV-2 antibody titres subside over time, COVID-19 breakthrough can and will occur. This is already seen in vaccinated, healthy individuals (Shrotri et al., 2021). This is further complicated as SARS-CoV-2 variants appear that have increased infectivity and immune-escape features requiring more antibody to neutralize infection, compared to the initial SAR-CoV-2 strain (Uriu et al., 2021). As CD20-treated individuals often produce lower titre antibody responses than untreated controls (Achiron et al., 2021;

Table 2
CD19 B cell repletion following administration of cladribine tablets.

Treatment	Time fromTreatment Onset	Number of% CD19 B cells of total lymphocytes/total		
		1% B cells	2% B cells	3% B cells
Cladribine cycle1	0 weeks	82/82 (100%)	82/82 (100%)	81/82 (99%)
	5 weeks	75/76 (99%)	73/76 (96%)	61/76 (80%)
	9 weeks	65/72 (90%)	42/72 (58%)	26/72 (36%)
	13 weeks	70/72 (97%)	62/72 (86%)	47/72 (51%)
	16 weeks	76/77 (99%)	70/77 (91%)	60/77 (78%)
	24 weeks	77/77 (100%)	75/77 (97%)	70/77 (91%)
Treatment	Time from Treatment	Number of PwMS with indicated number of CD19+ B cells		
		>5 cells µl	>10cells/µl	>20 cells/µl	>30 cells/µl
Cladribine cycle 1	0 weeks	81/81 (100%	81/81 (100%	81/81 (100%	81/81 (100%
	5 weeks	76/76 (100%)	73/76 (96%)	63/76 (83%)	60/76 (79%)
	9 weeks	68/72 (94%)	51/72 (71%)	31/72 (43%)	21/72 (29%)
	13 weeks	74/76 (97%)	71/76 (93%)	59/76 (78%)	42/76 (55%)
	16 weeks	77/77 (100%)	74/77 (96%)	66/77 (86%)	59/77 (77%)
	24 weeks	78/78 (100%)	77/78 (99%)	74/78 (95%)	66/78 (84%)

Individuals received 0.875 mg/kg cladribine tablets over 1 week and this was repeated one month later. The information was extracted from the phase III trial data supplied by the European Medicines Agency (Gibiansky et al., 2021). The second cycle of cladribine was not adjusted to lymphopenia as occurs in the licenced dosing schedule and is therefore not shown. The results represent the approximate time from the onset of treatment and report the frequency of people reaching 1%, 2% or 3% CD19 of total lymphocyte count or the number of cases with absolute number of peripheral blood CD19+ B cells above the cell count. The data was calculated from B cell numbers reported as cells/µl and lymphocyte data reported to cells $x10^9$/l to two decimal places. PwMS people with multiple sclerosis.

Table 3
CD19 B cell repletion following alemtuzumab infusion.

Treatment	Time fromlast infusion	Number of% CD19 B cells of total lymphocytes/total analysed		
		1% B cells	2% B cells	3% B cells
Alemtuzumab cycle 1	0 weeks	362/362 (100%)	362/362 (100%)	362/362 (100%)
	1 month	365/365 (100%)	214/365 (59%)	156/365 (43%)
	3 months	368/368 (100%)	368/368 (100%)	368/368 (100%)
	6 months	372/372 (100%)	372/372 (100%)	372/372 (100%)
Alemtuzumab cycle 2	1 months	367/367 (100%)	292/367 (80%)	234/367 (64%)
	3 months	367/367 (100%)	366/367 (100%)	366/367 (100%)
	6 months	374/374 (100%)	374/374 (100%)	374/374 (100%)
Treatment	Time from last infusion	Number of PwMS with indicated number of CD19+ B cells		
		≥10 cells/µl	≥20 cells/µl	≥30 cells/µl
Alemtuzumab cycle 1	0 weeks	Insufficient data to calculate	362/362 (100%)	362/362 (100%)
	1 month		365/365 (100%)	23/365 (6%)
	3 months		368/368 (100%)	368/368 (100%)
	6 months		372/372 (100%)	372/373 (100%)
Alemtuzumab cycle 2	1 months		367/367 (100%)	71/267 (19%)
	3 months		367/367 (100%)	360/367 (98%)
	6 months		374/374 (100%)	372/374 (99%)

Individuals received 60 mg alemtuzumab (cycle 1) and 36 mg alemtuzumab (cycle 2) twelve months later. The information was extracted from the phase III CARE-MS 1 (treatment naïve) and the CARE-MS 2 (prior beta interferon treatment) trial data (Baker et al., 2017a) supplied by the manufacturer via the clinicalstudydatarequest.com portal. The results represent the approximate time from the onset of treatment and report the frequency of people reaching 1%, 2% or 3% CD19 of total lymphocyte count or the number of cases with an absolute number of peripheral blood CD19+ B cells above the cell number shown. These were reported to two decimal places reported as a percentage of lymphocytes or absolute number as cells $x10^9$/l. The minimum number of cells reported was therefore 20 cells/µl. The percentage lymphocytes was reported to no decimal places. PwMS people with multiple sclerosis.

Sormani et al., 2021b; Tallantyre et al., 2021), they are potentially in particular need of effective booster (third cycle) vaccinations to limit infection. However, it is clear that the majority of CD20-depleted individuals, even in those with low antibody titres, generate robust CD4 and CD8 anti-viral T cell responses following the initial vaccination that can provide protective immunity following infection (Madelon et al., 2021; Apostolidis et al., 2021; Gadani et al., 2021; Brill et al., 2021). Whilst booster vaccines may increase seroconversion and augment existing immune responses in some immunocompromised people, CD20 depletion can still inhibit booster responses as already seen in MS and other conditions using rituximab (Connolly et al., 2021; Greenberger et al., 2021; Re et al., 2021; König et al., 2021; Sidler et al., 2021), particularly in those who failed to seroconvert after two vaccine doses (König et al., 2021; Sidler et al., 2021). A solution may be to provide a high-titre antibody response through monoclonal antibody cocktails or use of convalescent sera in high-risk individuals (Hurt and Wheatley, 2021). Furthermore, anti-viral agents are being developed (Lee et al., 2021), which could help augment the protective effect of any immunity in immunosuppressed individuals. It remains to be seen to what extent vaccine-induced T cell responses and biological and chemical anti-viral agents are sufficient to protect CD20-depleted individuals. However, maximising the chance of an effective response to vaccination in immunosuppressed people should be a priority, if it is safe to do so. It is evident that CD19 B cells recover rapidly following cladribine and alemtuzumab (Gibiansky et al., 2021; Baker et al., 2017a) and this is probably consistent with a robust COVID-vaccine response in most people if vaccination in undertaken once immune-reconstitution occurs (Achiron et al., 2021; Sormani et al., 2021b; Tallantyre et al., 2021). However based on the B cell repopulation kinetics and poor vaccine response, one could argue that delaying treatment for a short period to facilitate the most-effective booster programme possible may be a justifiable risk, based on this uncontrolled trial data, which suggested comparable annualised relapse rate and disease breakthrough during the treatment-delayed period to that seen in other studies during continuous treatment (Baker et al., 2020a), and notably the experience with treatment delays during the COVID-19 pandemic (Maarouf et al., 2020; Rolfes et al., 2021; van Lierop et al., 2021; Baker et al., 2021). However, unless controlled-studies are conducted to demonstrate safety, it may be too late to inform on and optimize the next stage of vaccination process/COVID-19 control in ocrelizumab-immunosuppressed people with multiple sclerosis.

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CRediT authorship contribution statement

David Baker: Conceptualization, Writing – original draft, Formal analysis, Writing – review & editing. **Amy MacDougall:** Formal analysis, Writing – review & editing. **Angray S. Kang:** Conceptualization, Writing – review & editing. **Klaus Schmierer:** Conceptualization, Writing – review & editing. **Gavin Giovannoni:** Conceptualization, Writing – review & editing. **Ruth Dobson:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

DB, KS, GG RB, have received compensation for consultancy/educational activity from Roche/Genentech, Merck, and/or Sanofi/Genzyme who manufacture COVID-19 and MS drugs discussed in this study. These were not involved in the content or the decision to publish. AM, AK have nothing relevant to declare. Although considered irrelevant DB, KS, GG, RB have received compensation for consultancy/educational activity from all companies manufacturing licenced disease modifying agents in the MS space.

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