Anti-CD20 Cell Therapies in Multiple Sclerosis—A Fixed Dosing Schedule for Ocrelizumab is Overkill

Drug Target Insights
Volume 11: 1–3

DOI: 10.1177/1177392817737515

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ABSTRACT: Anti-CD 20 therapies have found significant uses in multiple sclerosis (MS). Based singularly on the accumulated evidence with the use of rituximab (RTX; Rituxan, Genentech, and Biogen) in neuroimmunological diseases, ocrelizumab (OCR; Ocrevus, Genentech) was developed as a treatment option for MS and selectively targets CD20 B cells, a cell surface antigen found on pre-B cells, mature, and memory B cells, but not on lymphoid stem cells and plasma cells. On the basis of indirect evidence, elimination of the antigen-presenting capabilities and antigen nonspecific immune functions of B cells appear to be central to the therapeutic efficacy of anti-CD20 B-cell therapies. An important question is this—Why does the drug need to be dosed at fixed intervals and not ***based*** on a measurable endpoint, such as tracking peripheral CD20 cell counts? There is minimal scientific validity in infusing the drug every 6 months particularly if CD20 cell counts are negligible in the peripheral blood. In this analysis, a case is made for following CD19 cell populations as a surrogate for CD20 cells on a monthly basis to guide OCR redosing parameters and does not follow a scheduled dosing parameter.

KEYWORDS: Ocrelizumab, Multiple Sclerosis, CD19/20 cells, anti-CD therapies, Rituxan, Dosing schedules, Ocrevus, Neuromyelitis optica spectrum disorder

RECEIVED: June 30, 2017. **ACCEPTED:** September 4, 2017.

PEER REVIEW: Two peer reviewers contributed to the peer review report. Reviewers' reports totaled 230 words, excluding any confidential comments to the academic editor.

TYPE: Rapid Communication

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Background and Introduction

In March 2017, ocrelizumab (OCR) was approved by the Food and Drug Administration (FDA) for the treatment of relapsing forms of multiple sclerosis (MS) and primary-progressive multiple sclerosis. It is a humanized anti-CD20 monoclonal antibody (MAb) molecule that leads the MAb revolution in the treatment of MS. To understand OCR and its pharmacodynamics, a closer look at rituximab (RTX) helps one to decode OCR dosing. Published literature suggests that RTX is a chimeric (human/murine) MAb directed against the human CD20 molecule[1] and promotes cytotoxicity and apoptosis. It was approved by the FDA for the treatment of rheumatoid arthritis (RA) in 2006 and was the first therapeutic B-cell–depleting chimeric MAb to be used in MS with success. Diseases such as MS, RA, neuromyelitis optica/neuromyelitis optica spectrum disorder (NMO/NMOSD), systemic lupus erythematosus, peripheral neuropathies, antimyelin-associated glycoprotein neuropathy, chronic inflammatory demyelinating polyneuropathy, subacute ataxic neuropathy without paraproteinemia, myasthenia gravis, opsoclonus-myoclonus syndrome, and inflammatory myopathies have been treated using anti-CD20 MAbs. Both OCR and RTX bind to an extracellular CD20 epitope on B cells whose binding site overlaps between each drug.

Following CD19 cell counts as a surrogate marker for CD20 cells in the peripheral blood in patients with RA, NMOSD, and MS on RTX therapy helps us understand how the dosing of OCR dosing may be optimized in the treatment of MS. In general, RTX treatment produces a rapid depletion of CD20 cells from the circulation but does not directly target pro-B cells, their precursors, or plasma cells.[2–3] As RTX interferes with flow cytometric analysis of CD20 cells, CD19 cells, which carry a similar expression profile, are typically used as surrogate markers to schedule reinfusion based on CD19 cell counts. It is thought that RTX binding to CD20 enables cells to mediate trogocytosis or "shaving" causing internalization of the RTX-CD20 complex and accompanying cell membrane through an Fcγ receptor–dependent mechanism[4–5]—this process is thought to interfere with the flow cytometric analysis of CD20 cells, and therefore, CD19 cell counts serve as the surrogate marker to monitor treatment efficiency of anti-CD20 cell therapies. The depth of B-cell depletion is variable among patients, but restoration of the B-cell repertoire takes between 9 and 12 months from the last perfusion of RTX.[6]

In patients with RA, treatment with RTX induces depletion of peripheral B lymphocytes, with many patients demonstrating near complete depletion (CD19 counts are <20 cells/μL or below the lower limit of quantification) within 2 weeks after receiving the first dose of the drug. Some patients show peripheral B-cell depletion that lasts for at least 6 months. Up to ~4% of patients with RA had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of RTX. Equally important, some patients may need more infusions than a 6-month re-administration schedule. The reconstitution of peripheral blood B cells after RTX therapy in patients with RA was noted after a mean of 8 months posttreatment.[7]

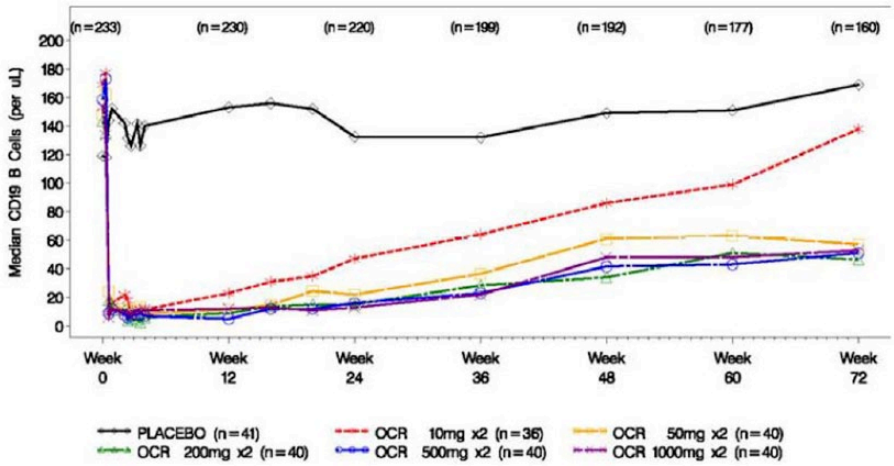

Figure 1. Median peripheral blood B-cell profiles following intravenous ocrelizumab (OCR) administration in subjects with rheumatoid arthritis in study ACT2847g.

In a study involving 107 patients with MS, 105 (98.1%) had at least 1 follow-up CD20 count after the first RTX administration and follow-up levels occurred at an average of 138.3 ± 121.4 days apart.[8] The CD20 counts of patients who received 1000 mg with a concurrent 1000 mg dose 2 weeks later were above 0 by 6 months in 20% of patients, whereas 3% of patients had a CD20 count above 2% of baseline numbers. Of patients receiving a single RTX 1000 mg dose, 20% had a CD20 count above 0 by 6 months, and 5% of patients had >2% by 6 months. This small, observational study in one MS care clinic clearly showed how widely different the repopulation of CD20 counts were, suggesting that a fixed time scheduling is perhaps not optimal. Given the wide spectrum of unpredictable B-cell suppression, it is impossible to predict how each individual patient would respond to RTX and what the optimal dosing interval ought to be in each patient. A more obvious question is whether scheduled RTX infusions are required when CD20 counts are negligible—what is the target cell when counts are less than 20 cells/μL and what is the rationale for reinfusion? There are no hard data to support this treatment regimen.

In another disease model, the treatment of NMO/NMOSD with RTX tightly scheduled every 6 to 9 months to prevent relapses was not globally successful either[9–11] casting doubt on the theory that treatment protocols should follow a scheduled dosing pattern. In addition, Greenberg and colleagues[9] retrospectively reviewed RTX dosing in an NMO clinical cohort and concluded that patients should be redosed prior to evidence of B-cell reconstitution by CD20 counts which is probably optimal and individualized.

Pellkofer and colleagues also reviewed RTX experience in patients with NMO, and based on their results concluded that a fixed dosing schedule every 69 months was advisable.[11] Studies have also shown that drugs such as RTX also deplete anti-CD20 T cells demonstrating that peripheral depletion of all CD20 cells contributes to suppression of disease.[12] Taken together, studies in RA, MS, and NMOSD have demonstrated why a fixed dosing schedule with RTX may not be optimal. In the case of RTX, the package insert clearly notes that redosing for patients with RA is based on (1) clinical evaluation or (2) every 24 weeks. However, no such options exist for the use of OCR in patients with MS and dosing schedules are fixed.

Discussion

The scheduled dosing of OCR for both forms of MS is slated at 6-month intervals. Because OCR avidly targets CD20 cell populations and depletes them and as their numbers can be monitored by peripheral blood counts of CD19 cells, it remains poorly understood why OCR needs to be reinfused at scheduled intervals regardless of CD20 cell counts. In addition, in up to 1% (12/1311) of all patients with MS in clinical trials, relapsing and primary-progressive types, antidrug antibodies (ADAs), and particularly neutralizing antibodies appeared in 2 patients, clearing OCR faster and rendering B-cell repletion quicker. This is one other reason why following CD20 cells are prudent. Additional validity and strength of my analysis come from the original data submitted to the Center for Drug Evaluation and Research as shown in Figures 1 and 2 which depict CD19 cell populations in clinical trials at <20 cells/μL, the lower limit of quantification, at 24 weeks postinfusion. These results are derived from the Clinical Pharmacology and Biopharmaceutics Review (application no. 761053Orig1s000), the document that was originally submitted to the FDA for evaluation and approval of Ocrevus. Finally, in the package insert for OCR, one of the statements warns not to administer subsequent doses if the separation between doses is not at least 5 months. This statement is pithy but ignores the fact that repopulation of CD20 cells could also remain undetectable at 6 months postinfusion. Hence, to correctly assess the need to reinfuse, following monthly CD19 cell counts is a small price to pay both in the scientific and literal sense. In addition, data on long-term OCR therapy are lacking and concern regarding prolonged B-cell depletion remains; these could come to light in postmarketing data.

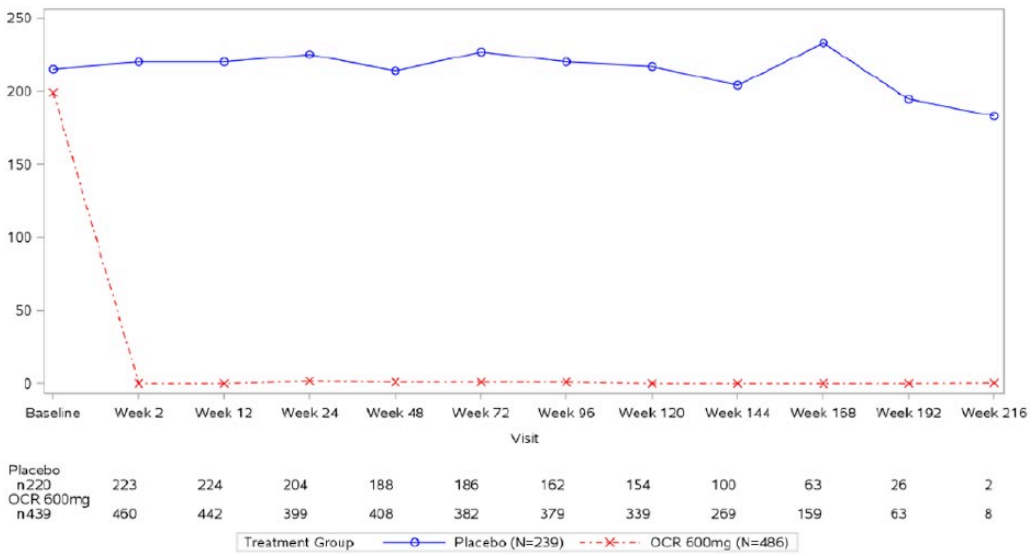

Figure 2. Median B-cell count in study WA25046 (primary-progressive multiple sclerosis). OCR indicates ocrelizumab.

Specifically, OCR is an expensive biologic that promises to deliver clinical benefit. However, the long-term safety of repeated OCR treatment remains unknown and there is no scientific validity to giving the drug when CD20 cells are nonexistent in the periphery at counts below 20 cells/μL. Any effective treatment strategy that aims to minimize unnecessary patient exposure to the drug helps with patient safety and allows for significant cost savings to the patient and third-party payers.

Therefore, the following recommendations are suggested. (1) If the disease activity stabilizes both clinically and from a radiological perspective, less frequent retreatment might be sufficient to prevent relapses, although the correlation between clinical/radiological criteria to disease activity is not a linear relationship and therefore must be individualized based on monthly CD20 cell counts by monitoring CD19 cells. (2) Alternatively, CD20 cell counts must be monitored monthly on a routine basis irrespective of clinical or radiological status and reinfusion of the drug carried out after the cell population rebounds to ≥20 cells/μL; this holds true also for patients who develop ADAs that can neutralize OCR activityin which case the CD19 cell count would repopulate.

Author Contributions

JA: Idea/conceptualization, data collection/collation and analysis, as well as write-up of the manuscript and submission.

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