Different lymphocyte counts of multiple sclerosis patients treated with ofatumumab and ocrelizumab: A retrospective observational study

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ABSTRACT

INTRODUCTION: Patients with Multiple Sclerosis (pwMS) treated with anti-CD20 (cluster of differentiation) monoclonal antibodies (mAbs) such as ocrelizumab (OCR) and ofatumumab (OFA) show a reduction mainly of B-lymphocytes, but also other lymphocyte subsets can be affected by these treatments. There is limited data on differences between lymphocyte subset counts of pwMS after treatment initiation with OCR or OFA.

OBJECTIVE: To compare lymphocyte subset counts after treatment initiation in pwMS treated with OCR and OFA.

METHODS: We analyzed 22 pwMS initiated on OFA and 56 sex-, age- and MS course matched pwMS initiated on OCR from 2 prospectively collected observational MS databases (Bern [n: OFA 14, OCR 44] and Vienna [n: OFA 8, OCR 12]) statistically comparing lymphocyte subset counts (Mann Whitney Test).

RESULTS: We found that pwMS treated with OCR showed a stronger reduction of CD20 B-lymphocytes ($P = .001$), and a trend towards lower counts of $CD8^+$ T cells ($P = .056$) compared to pwMS treated with OFA, whereas reduction of total lymphocyte, $CD4^+$ lymphocyte and NK cell count was equally distributed between both treatments.

CONCLUSION: Different effects on lymphocyte subpopulations appear to be present in pwMS after treatment initiation with different anti-CD20 mAbs. Further studies are needed to determine potential effects on anti-CD20 treatment efficacy as well as treatment associated risks such as failed vaccinations and infections.

KEYWORDS: Immunotherapy, MS, anti-CD20, aCD20, ocrevus, kesimpta, white blood cells

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Introduction

Among the multitude of disease-modifying therapies (DMT) available for patients with Multiple Sclerosis (pwMS), B cell depleting anti-cluster of differentiation 20 (CD20) monoclonal antibodies (mAbs) such as ocrelizumab (OCR) and ofatumumab (OFM) represent highly effective options to reduce relapse rate, magnetic resonance imaging (MRI) activity and, to a certain extent, progression of the disease.[1-3] Clinical efficacy supports the relevance of B cells in pathophysiology of MS has been well documented, both in the periphery and in the central nervous system (CNS).[4-7]

B cells contribute to multiple immune reactions in pwMS, such as promotion of T-cell activation and proliferation as antigen-presenting cells (APC), interaction with APC to influence antigen trafficking, production of cytokines and chemokines, leading to glial and neuronal damage.[8] CD20 is a transmembrane, non-glycosylated phosphoprotein expressed in tetramers on the surface of large parts of the B cell lineage from pre-B cells to naïve and memory B cells, but neither on the very early part (stem cells, pro-B cells) nor on the very late part of the B cell lineage (plasmablasts and plasma cells).[9] Therefore, both early and late maturation stages of B cells are not depleted by anti-CD20-mAbs, thus potential for B-cell repopulation and to a different extent humoral immune memory are preserved.[8] CD20 is not only found on B cells, but also on a subset of T cells, especially in autoimmunity.[10] In pwMS, OCR seems to have multiple influences on memory $CD8^+$ T cells.[11]

OFA is a fully human IgG1-anti-CD20 antibody, whereas OCR is a humanized antibody.[8] Human CD20 consists of a smaller and a larger extracellular loop. The binding epitope of OCR and RTX is on the larger extracellular loop of CD20, whereas OFA binds to both the larger and the smaller extracellular loop of CD20.[12] Anti-CD20-mAbs deplete B cells via apoptosis, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis, and complement-dependent cytotoxicity (CDC).[13] In comparison to OCR and RTX, OFA exhibits greater CDC than ADCC. It is hypothesized that this allows a lower dosing compared to other anti-CD20-mAbs.[13] If the above mentioned differences in CDC and ADCC result in different clinical outcomes or if this is due to the different routes of application (s.c. vs iv.) with a higher concentration in the lymphatic system after s. c. Application is not known.[13,14]

Still comparative data on the development of lymphocyte subset counts under treatment with OCR or OFA is lacking. Thus, this paper aims to describe the effect of treatment initiation with OFA and OCR on different lymphocyte subpopulation counts in pwMS.

Methods

Patient cohort

In this retrospective observational study, we included data from 2 prospectively collected observational MS databases (Inselspital, University Hospital Bern, Switzerland and Vienna MS database, Department of Neurology, Medical University of Vienna, Austria). We extracted pwMS treated with OFA and available lymphocyte subset counts and compared them with 1 to 3 age-, sex- and MS course-matched pwMS treated with OCR and available lymphocyte subset counts.

Only blood values after the second infusion of 300 mg OCR or after the third injection of 20 mg OFA were included. We compared the following lymphocyte subpopulations: total lymphocyte count, B cell, $CD4^+$ T cell and $CD8^+$ T cell count as well as natural killer (NK) cell counts. In addition, the following clinical data was extracted: age, sex, disease duration (years), type of MS diagnosis, and type of previous MS treatment(s). Analysis of lymphocyte subpopulations were performed directly after sampling by the respective central laboratories of each university hospital.

Statistical analysis

Continuous variables were given as mean (95% confidence interval (CI); range) or median (interquartile range, range), and categorical variables were given as absolute number and frequencies. Mann–Whitney U, and Fisher's exact tests were used for comparative statistics with a level of significance of .05 and for a trend of .10. Due to heterogeneity in pre-treatments, we performed a subgroup analysis of findings in patients that were untreated prior to initiation of OFA or OCR. Here we used a one-tailed statistical approach as the direction of the difference (greater or small than) is known from the previous analysis of all patients. As measurement of effect size the determination coefficient R2 was calculated as follows: $r^2 = (z^2)/N$.

Results

Patient characteristics

In our analysis, we included 22 pwMS treated with OFA (Bern 14, Vienna 8) and matched them with 56 pwMS treated with OCR (Bern 44, Vienna 12). In both cohorts, all patients had a relapsing remitting MS type and most of them were female. Differences were found in EDSS at treatment initiation, which was higher in OCR treated patients, and the time between treatment start and last EDSS, which was also longer in RRMS patients receiving OCR (Table 1).

Lymphocyte subpopulations after treatment initiation with OCR or OFA

No differences were found in total lymphocyte, NK cell and CD4 T cell counts between OCR and OFA treated pwMS. However, OCR treated pwMS had lower B cell counts (median (range): OCR .0 (0-178) vs OFA .5 (0-16), $r^2 = .034$, $P = .0012$) and a trend towards lower CD8 T cell counts (median (range): OCR 385 (72-1163) vs OFA 430.5 (110-1527), $r^2 = .01$, $P = .076$; Figure 1, Table 2). These group differences remained

Table 1. Patient characteristics at baseline.

	OCR (N = 56)	OFA (N = 22)	*P*-VALUE
Age, years (mean, 95% CI)	38.4 (35.4–41.5)	34.7 (29.2–40.2)	.22
Female sex (%)	41/56 (73)	16/22 (73)	.74
RRMS, n (%)	56/56 (100)	22/22 (100)	n.a
Time since diagnosis, y	5.6 (3.9–7.2)	4.2 (1.6–6.8)	.29
Previous DMT			
Number of different DMT, (median, min-max)	1 (0-4)	1 (0-6)	.16
None, n (%)	20/56 (36)	9/22 (41)	.30
Interferons, n (%)	2/56 (4)	1/22 (5)	
Glatiramer acetate, n (%)	2/56 (4)	1/22 (5)	
Teriflunomide, n (%)	1/56 (2)	3/22 (14)	
Dimethyl fumarate, n (%)	6/56 (11)	5/22 (23)	
Fingolimod, n (%)	9/56 (16)	1/22 (5)	
Ozanimod, n (%)	1/56 (2)	0/22 (0)	
Natalizumab, n (%)	12/56 (21)	2/22 (9)	
Rituximab, n (%)	2/56 (4)	0/22 (0)	
Daclizumab, n (%)	1/56 (2)	0/22 (0)	
EDSS score before Tx start (median, min-max)	2.5 (0–6.5)	2.0 (.0–5.0)	.04
EDSS score last after Tx start (median, min-max)	2.0 (.0–7.0)	1.5 (.0–5.0)	.10
Time between EDSS assessment before and the last after Tx start (years)	2.4 (2.0-2.7)	.8 (.7–1.0)	<.001

Statistic: Mann Whitney and Chi2 Test were performed. Abbreviations: DMT: disease-modifying therapies; EDSS: expanded disability status scale; n.a.: not available; n: number; OCR: ocrelizumab; OFA: ofatumumab; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis, Tx: Therapy.

statistically significant even after limiting the follow up period in the OCR treated patients to the maximum follow up time of the OFA group, which was 1.5 years (Table 2 and legend for information on n numbers of the OCR group with limited follow up period).

To account for different pretreatments we analyzed B and CD8 T cell counts in patients untreated prior initiation of OFA/OCR, despite small sample sizes (OFA n = 9, OCR n = 20) a trend towards higher B cell counts in OFA treated patients was seen in one-tailed statistics (mean rank: OCR 50.2 vs OFA 59.2, r^2 = .02, P = .07), which was not present for CD8 T cells (mean rank: OCR 53.38 vs OFA 46.62, r^2 = .01, P = .18).

Discussion

This study provides real-world evidence on lymphocyte subpopulation counts after treatment initiation with OFA or OCR in pwMS and highlights differences between both CD20 targeting therapies. Our main finding are lower B cell counts and a trend towards lower CD8 T cell counts in pwMS treated with OCR compared to OFA.

The lower B cell counts seen in pwMS treated with OCR in comparison to OFA in our cohort could have an effect on the therapeutic efficacy of the DMT. There is no generally accepted cut-off for therapeutic B-cell depletion and expert opinion suggests a cut-off of <10 cells/μL or <1% of total lymphocyte count.[15-18] However, even a lower degree of B-cell depletion seems to be clinically effective, as a B-cell depletion with OFA under a cutoff of 32 CD19 B cells/μL resulted in ⩾90% suppression of gadolinium-enhancing lesions.[19] Studies on extended interval dosing of OCR during the COVID-19 pandemic with a reinfusion threshold of ≥10 CD19 B cells/μL and a median re-dosing interval of 34 weeks (interquartile range 30-38) showed no clinical and only minimal paraclinical activity.[15] On the other hand, data on OCR suggests greater risk reduction on confirmed disability progression in patients with higher OCR exposure, leading to greater B cell depletion.[20]

In the pivotal studies, the subcutaneous administration of OFA resulted in a rapid and sustained reduction in B cells as early as 2 weeks after treatment initiation. After discontinuation of OFA, B cells returned to normal levels in at least 50% of pwMS within 24 to 36 weeks .[1] Similarly to OFA, infusion of OCR results in a rapid and sustained reduction in B cells as early as 2 weeks after treatment (first time point of measurement). Median time to B-cell repletion after cessation of OCR infusions was 72 weeks (range 27-175).[21] Although a definite cut-off for therapeutic B-cell depletion is not defined, expert opinion suggests a cut-off of <10 cells/μL or <1% of total lymphocyte count.[15-18]

This paper aims to describe the effect of treatment initiation with OFA and OCR on different lymphocyte subpopulation counts in pwMS. The trend towards a lower count of CD8 T cells seen in pwMS treated with OCR in comparison to OFA in our cohort could be particularly relevant, as it has been shown that CD8 T cells in pwMS treated with OCR are not

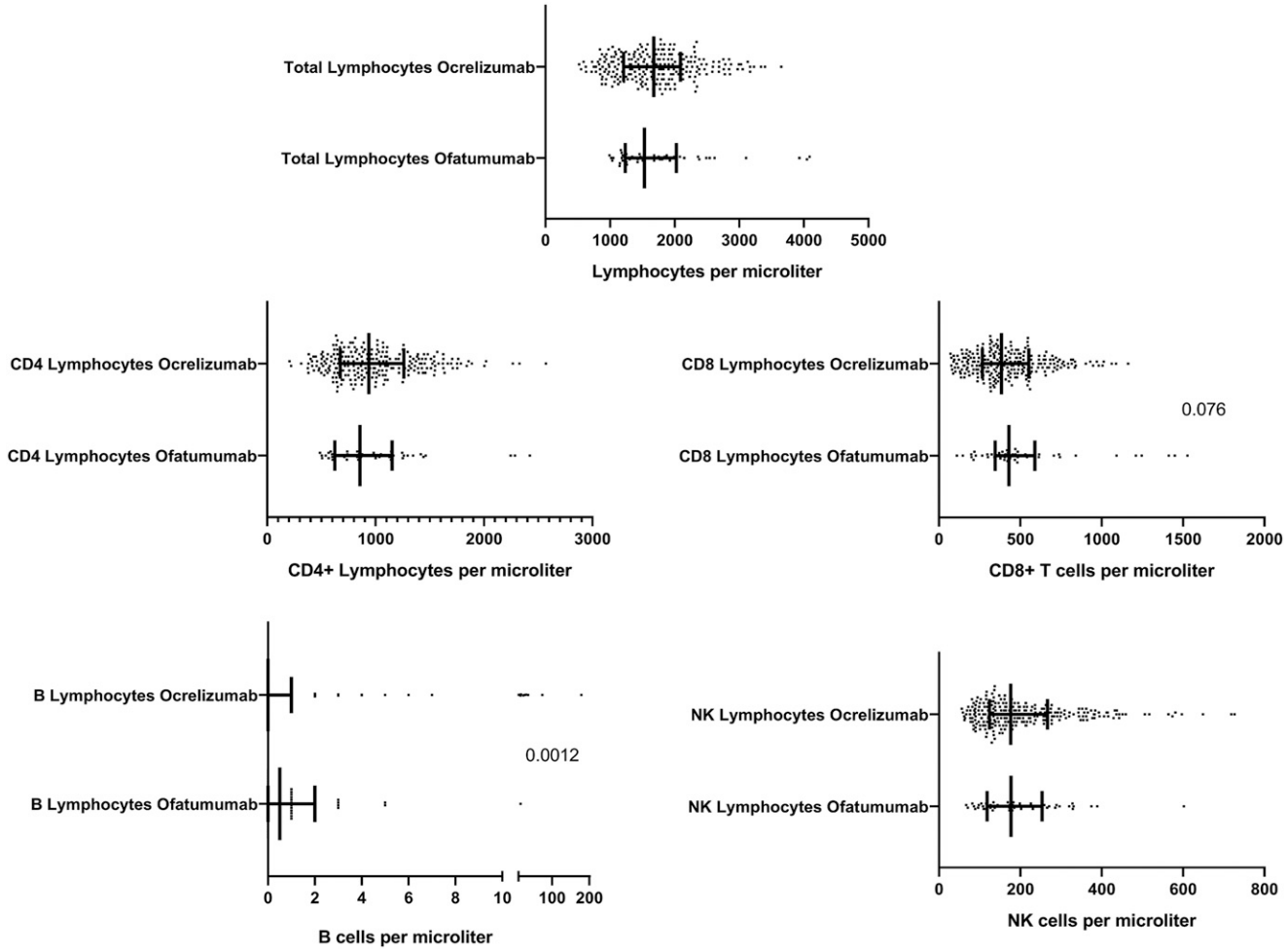

Figure 1. Lymphocyte subpopulation counts (median and interquartile range) in RRMS patients treated with OCR or OFA. Statistic: Mann Whitney Test; Abbreviations: CD: Cluster of Differentiation; NK: Natural Killer.

Table 2. Lymphocyte Subpopulations (median, min-max) after treatment initiation with OCR or OFA.

	OCRELIZUMAB	OFATUMUMAB	*P*-VALUE
Time since therapy initiation (FU, years)	1.34 (.03 – 4.62)	.59 (.1 – 1.5)	<.001
FU: OCR limited to max FU OFA, years	.75 (.03 – 1.5)	.59 (.1 – 1.5)	.2762
Total lymphocytes	1676.5 (521–3651)	1531.5 (990–4090)	.9559
Total B cells	.0 (0–178)	.5 (0-16)	.0012
B Cells: OCR limited to max FU OFA	.0 (0–178)	.5 (0-16)	.0319
Total CD8 cells	385 (72–1163)	430.5 (110–1527)	.076
CD8 cells: OCR limited to max FU OFA	374.5 (77–1163)	430.5 (110–1527)	.0538
Total CD4 cells	937 (205–2570)	856.5 (488–2423)	.3521
Total NK cells	176 (56–727)	177 (67–602)	.5946

In the OCR group 250 analyses and in the OFA group 52 analyses were included. After limiting the OCR follow up time to the maximal follow up time during OFA treatment, the number of included analyses of the OCR group dropped to 138. This was done to re-analyze lymphocyte differences taking into account different follow-durations of the whole cohort. Significant *P*-values are highlighted in bold. Statistic: Mann-Whitney Test was used. Abbreviations: CD: cluster of differentiation; d: days; FU: Follow up; n: number; NK: natural killer; OCR: Ocrelizumab; OFA: Ofatumumab, 95% CI: 95% Confidence Interval.

only depleted, but also impaired in phenotype, leading to a reduced migratory function.[2] Anti-CD20-mAbs can deplete activated myelin-specific CD8 T cells in MS, which highlights the potential therapeutic relevance of those cells.[22] This could contribute to the clinical efficacy of CD20 targeting drugs.[22] An alteration of the T cell compartment with a decreased CNS-migratory capacity of T cells has recently also been described for OFA.[23] In mice, CD20 expressing T cells are unable to endogenously express CD20 and their development requires CD20-expressing B cells.[24] Both murine and human T cells seem to acquire CD20 from B cells via trogocytosis while being activated from an antigen-presenting cell. Interestingly, the same authors showed, that an exclusive therapeutic depletion of CD20 T cells is able to ameliorate an experimental autoimmune encephalomyelitis (EAE) independently of B cells.[24] On the other hand, it is unlikely, that the removal of CD20 expressing T cells is the sole explanation of therapeutic efficacy of anti-CD20-mAbs, as B-cell targeting with anti-CD19 therapies, such as inebilizumab, also has a positive impact on MS activity.[25] Additionally, CD8 T cell decrease may be more pronounced in OCR treatment in pwMS with lymphopenia.[26] If a lower count of CD8 T cells of pwMS treated with OCR compared to OFA translates to further clinical or paraclinical outcomes should be investigated in the future.

In addition to efficacy, safety of anti-CD20-mAbs has to be considered. Regarding B cell depletion, the slight difference in B cell counts between OFA and OCR treated MS patients might contribute to a better humoral vaccination response in people treated with OFA compared to OCR seen in a small retrospective study.[27] Regarding $CD8^+$ T cells, antiviral responses have to be taken into account. A lower count of $CD8^+$ T cells might increase the risk of severe viral infections, such as the rarely reported progressive multifocal leukoencephalopathy (PML),[28] which was first seen in an elderly patient with primary progressive MS with lymphopenia treated with OCR, and also for the rare but severe enterovirus meningoencephalitis cases in patients with anti-CD20-mAbs.[29]

Main limitation of our work is the different follow up time between pwMS treated with OCR and OFA, which was longer in OCR treated patients. However, including only measurements within the maximum follow up time of the OFA cohort did not change our findings for B cells as well as CD8 positive T cells. As collected in clinical routine without standardized time intervals between OCR/OFA application and lymphocyte subpopulation analysis non-standardized sample collection represents a source of bias and potentially impacts the interpretation of our data. Pretreatments have to be considered, as 2 patients pretreated with rituximab were included in the OCR group. This might affect the lymphocyte subpopulations eg, by the prolonged administration of anti-CD20-mAbs or by affecting baseline lymphocyte counts[30]; however it also reflects the standard of care in the respective regions here Switzerland and Austria.

Furthermore, the small cohort size with different number of measurements per included patients and the different pretreatments, which were overall not significantly different distributed between cohorts, have to be considered as possible confounder. Moreover, lymphocyte data were not available for all patients prior to treatment initiation with B cell therapy, therefore we cannot rule out an effect of the prior immunotherapy on the measured lymphocyte counts after treatment initiation in those patients that received another treatment before OCR or OFA.[31] Thus, our work calls for reanalyzing these findings using the available data of the phase 3 clinical trials of OCR and OFA. Additionally, further studies are needed to establish if our findings with a different degree of B cell reduction translate in different clinical outcomes.

Conclusion

This study provides real-world evidence on lymphocyte subpopulation counts after treatment initiation with OFA or OCR in pwMS and exhibits lower B cell counts and a trend towards lower CD8 T cell counts in pwMS treated with OCR compared to OFA. Further studies are needed to establish if those findings have any clinical or even prognostic implications.

Author contributions

CF was responsible for the conceptualization, methodology, formal analysis, investigation and drafted the original and revised the manuscript. NK was responsible for collecting the data, conceptualization, and critically revising the manuscript. HH was responsible for methodology, drafting and critically revising the manuscript. SM was responsible for methodology, and critically revising the manuscript. TZ was responsible for collecting the data, investigation, and critically revising the manuscript. MEE was responsible for methodology and critically revising the manuscript. IK was responsible for conceptualization and critically revising the manuscript. PR was responsible for conceptualization and critically revising the manuscript. TB was responsible for conceptualization, methodology and critically revising the manuscript. AC was responsible for conceptualization, methodology and critically revising the manuscript. GB was responsible for the conceptualization of the study, formal analysis, investigation and review and editing of the manuscript. RH was responsible for the conceptualization of the study, formal analysis, investigation and review and editing of the manuscript. Christoph Friedli: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Nik Krajnc: Conceptualization, Data curation, Writing – review & editing, Helly Hammer: Methodology, Writing – original draft, Writing – review & editing, Stefanie Marti: Methodology, Writing – review & editing, Tobias Zrzavy: Data curation, Investigation, Methodology, Writing – review & editing, Maria Evangelopoulos: Methodology, Writing – review & editing, Ioanna Kapsali: Conceptualization, Writing – review & editing,

Paulus Rommer: Conceptualization, Writing – review & editing, Thomas Berger: Conceptualization, Methodology, Writing – review & editing, Andrew Chan: Conceptualization, Methodology, Writing – review & editing, Gabriel Bsteh: Conceptualization, Formal analysis, Investigation, Writing – review & editing, Robert Hoepner: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Writing – review & editing.

Ethics statement

This study was approved by the responsible ethic committees (Bern: BE 2017-01369, Vienna: EK 2323/2019). Because of the retrospective nature of the analysis with pseudonymized patient data, the requirement for separate informed consent was waived by the committee for patients included prior to introduction of the general consent. This is in accordance with the local legislation. For patients treated after the introduction of the general consent (February 2015), the availability of the patients' consent was confirmed before inclusion in the analysis.

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Data availability statement

Data and material are available upon reasonable request to the corresponding author.

REFERENCES

1. Hauser SL. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2016;376(3):221-234.
2. Montalban X. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220.
3. Hauser SL. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med*. 2020;383(6):546-557.
4. Li R, Patterson KR, Bar-Or A. Reassessing B cell contributions in multiple sclerosis. *Nat Immunol*. 2018;19(7):696-707.
5. Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple sclerosis: mechanisms and immunotherapy. *Neuron*. 2018;97(4):742-768.
6. Frischer JM. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain*. 2009;132(5):1175-1189.
7. Magliozzi R. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain*. 2007;130(4):1089-1104.
8. Margoni M. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. *J Neurol*. 2022;269(3):1316-1334.
9. Meyer S. New insights in Type I and II CD20 antibody mechanisms-of-action with a panel of novel CD20 antibodies. *Br J Haematol*. 2018;180(6):808-820.
10. Vlaming M. CD20 positive CD8 T cells are a unique and transcriptionally-distinct subset of T cells with distinct transmigration properties. *Sci Rep*. 2021;11(1):20499.
11. Mathias A. Ocrelizumab impairs the phenotype and function of memory CD8+ T cells. *Neurol Neuroimmunol Neuroinflamm* 2023;10:e200084.
12. Teeling JL. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol*. 2006;177(1):362-371.
13. Gelfand JM, Cree BAC, Hauser SL. Ocrelizumab and other CD20+ B-Cell-Depleting therapies in multiple sclerosis. *Neurotherapeutics*. 2017;14(4):835-841.
14. Migotto MA. Efficient distribution of a novel zirconium-89 labeled anti-cd20 antibody following subcutaneous and intravenous administration in control and experimental autoimmune encephalomyelitis-variant mice. *Front Immunol*. 2019;18(10):p2437.
15. van Lierop ZY. Personalized B-cell tailored dosing of ocrelizumab in patients with multiple sclerosis during the COVID-19 pandemic. *Multiple Sclerosis Journal*. 2022;28(7):1121-1125.
16. Tazza F. Personalizing ocrelizumab treatment in Multiple Sclerosis: what can we learn from Sars-Cov2 pandemic? *J Neurol Sci*. 2021;427:117501.
17. Zecca C. Treatment of multiple sclerosis with rituximab: a multicentric Italian–Swiss experience. *Multiple Sclerosis Journal*. 2020;26(12):1519-1531.
18. van Kempen ZL. Extended dosing of monoclonal antibodies in multiple sclerosis. *Multiple Sclerosis Journal*. 2022;28(13):2001-2009.
19. Bar-Or A. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis. *The MIRROR study*. 2018;90(20):e1805-e1814.
20. Kletzl H. Pharmacokinetics, pharmacodynamics and exposure-response analyses of ocrelizumab in patients with multiple sclerosis (N4.001). *Neurology*, 2019;92(15 Supplement):N4001.
21. Gibiansky E. Ocrelizumab in relapsing and primary progressive multiple sclerosis: pharmacokinetic and pharmacodynamic analyses of OPERA I, OPERA II and ORATORIO. *Br J Clin Pharmacol*. 2021;87(6):2511-2520.
22. Sabatino JJ. Anti-CD20 therapy depletes activated myelin-specific CD8(+) T cells in multiple sclerosis. *Proc Natl Acad Sci U S A*. 2019;116(51):25800-25807.
23. von Essen MR. Ofatumumab modulates inflammatory T cell responses and migratory potential in patients with multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4).
24. Ochs J. Proinflammatory CD20(+) T cells contribute to CNS-directed autoimmunity. *Sci Transl Med*. 2022;14(638):eabi4632.
25. Agius MA. Safety and tolerability of inebilizumab (MEDI-551), an anti-CD19 monoclonal antibody, in patients with relapsing forms of multiple sclerosis: results from a phase 1 randomised, placebo-controlled, escalating intravenous and subcutaneous dose study. *Mult Scler*. 2019;25(2):235-245.
26. Abbadessa G. Lymphopenia in Multiple Sclerosis patients treated with Ocrelizumab is associated with an effect on CD8 T cells. *Mult Scler Relat Disord*. 2022;60:103740.
27. Levit E, Longbrake EE, Stoll SS. Seroconversion after COVID-19 vaccination for multiple sclerosis patients on high efficacy disease modifying medications. *Mult Scler Relat Disord*. 2022;60:103719.
28. Patel A. Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with ocrelizumab monotherapy. *JAMA Neurol*. 2021;78(6):736-740.
29. Perriguey M. Hypogammaglobulinemia and infections in patients with multiple sclerosis treated with rituximab. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1).
30. Abbadesa G. CD19 cell count at baseline predicts B cell repopulation at 6 and 12 Months in multiple sclerosis patients treated with ocrelizumab. *Int J Environ Res Public Health*. 2021;18(15):8163.
31. Abbadesa G. Previous disease-modifying treatments influence T lymphocyte kinetics in people with multiple sclerosis switching to ocrelizumab. *J Neuroimmunol*. 2023:378:578072.