Presented at CMSC Annual Meeting 2022
June 1-4, 2022 • National Harbor, MD, USA

DMT55

A Systematic Literature Review of Immunoglobulin Levels Among B-Cell–Depleting Therapies and Risk of Infections in Relapsing Multiple Sclerosis

Shiv Saidha,[1] Judith Bell,[2] Sydney Harold,[2] Jose Marcano Belisario,[2] Emma Hawe,[2] Samantha (Qiujun) Shao,[3] Kerri Wyse,[3] Eric M. Maiese[3]

[1]Division of Neuroimmunology and Neurological Infections, Johns Hopkins Hospital, Baltimore, MD, United States; [2]RTI Health Solutions, Manchester, United Kingdom; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

SUMMARY

- Evidence identified in this literature review suggests that reduced IgG levels are associated with increased risk of infection in patients with MS.
- Among patients treated with ocrelizumab, IgG levels appear to decrease over time.
- Conversely, IgG levels did not decrease over time among patients treated with ofatumumab.
- IgM levels decreased over time for people taking either ocrelizumab or ofatumumab.
- IgA levels were reported in only 2 trial populations and suggested comparable trends to IgG.
- Additional research is needed to further understand the differences between ocrelizumab and ofatumumab, particularly longer-term RWE.

ACKNOWLEDGMENTS: This study was funded by Novartis Pharmaceuticals Corporation. Project management, editing, and design support were provided by Kate Lottman and Paul Hobson of RTI Health Solutions. This poster was developed in accordance with Good Publication Practice (GPP3) guidelines. Authors had full control of the content and made the final decision on all aspects of this poster.

DISCLOSURES: Dr. Shiv Saidha is a Professor in the Department of Neurology at the Johns Hopkins University School of Medicine. Shiv Saidha engaged in this research as a private consultant or advisor and not in his capacity as a Johns Hopkins faculty member. Shiv Saidha been compensated for a consulting or advising service by Novartis in income/honorarium. Shiv Saidha has received consulting fees from Medical Logix for the development of CME programs in neurology, and has served as a consultant for Novartis, Biogen, Genentech Corporation, Carl Zeiss Meditec, and Bristol Meyers Squibb. He is the PI of investigator-initiated studies funded by Genentech and Biogen, was the site investigator of a trial sponsored by MedDay Pharmaceuticals, and received support from the Race to Erase MS foundation. He has received equity compensation for consulting from JuneBrain LLC, a retinal imaging device developer. Eric Maiese, Kerri Wyse, and Qiujun (Samantha) Shao are employees of Novartis Pharmaceuticals Corporation.Judith Bell, Sydney Harold, Jose Marcano Belisario, and Emma Hawe are employees of RTI Health Solutions and worked as consultants to Novartis Pharmaceuticals Corporation.

Text : Q6054e
To : 8NOVA (86682) US Only
+18324604729 North, Central and South Americas; Caribbean; China
+447860024038 UK, Europe & Russia
+46737494608 Sweden, Europe
Visit the web at: http://novartis.medicalcongressposters.com/Default.aspx?doc=6054e

INTRODUCTION

- Selectively targeting B-cell depletion with anti-CD20 monoclonal antibodies has been proven highly effective at limiting disease activity in people with relapsing forms of multiple sclerosis (RMS).
- However, the B-cell depletion and resulting immunosuppression may lead to decreased immunoglobulin (Ig) levels and, consequently, increased risk of infection.
- Multiple clinical trials and real-world studies have reported Ig levels over time for patients with MS treated with ofatumumab and ocrelizumab. For example, the phase 3 ASCLEPIOS I/II study with safety data up to 4 years presented here (DMT04) showed that mean IgG levels remained similar to baseline values for patients who used ofatumumab.[1]
- Currently, ofatumumab and ocrelizumab are the only anti-CD20 monoclonal antibodies approved by the United States (US) Food and Drug Administration and the European Medicines Agency for the treatment of RMS.
- It is important to summarize these clinical trials and real-world evidence to better understand what is currently known about the change in Ig levels and risk of infection for patients treated with these B-cell depletion therapies.

OBJECTIVE

- To explore the change in Ig levels for people with RMS taking ocrelizumab or ofatumumab and the relationship between Ig levels and infections in people with MS.

METHODS

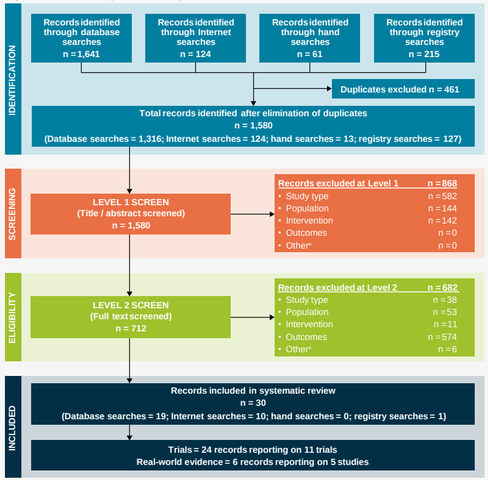
- A systematic literature review (SLR) was conducted to identify publications of trials and real-world evidence (RWE) studies that reported data on Ig levels over time for ocrelizumab and ofatumumab for people with RMS (including relapsing RMS and active secondary progressive MS).
  - Searches were conducted in Embase, MEDLINE, and Cochrane Library from initiation until 10 September 2021.
  - Searches were limited to English-language publications. Conference abstracts were limited to those published after 2017.
  - In addition, selected conference proceedings, bibliographies of identified SLRs and meta-analyses, trial registries, and regulatory websites were searched.
  - No formal quantitative analysis was feasible due to heterogeneity between studies and endpoints.
- A targeted literature review (TLR) of trials and RWE was also performed to consider the relationship between Ig levels and infection risk in people with any type of MS who were receiving any intervention.

RESULTS

SLR Results

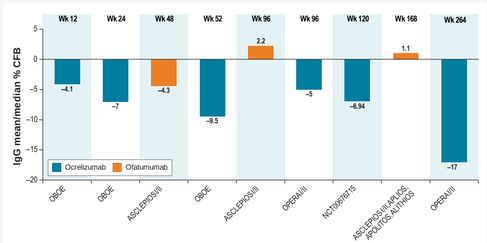
- Of the 1,580 articles identified in the SLR, 30 publications met the inclusion criteria (Figure 1).
- 24 of the included publications reported data on 11 clinical trials. However, some trials were reported only as pooled data with other trials. Therefore, results from 9 trial populations were included, 5 with ofatumumab and 4 with ocrelizumab (Table 1).
- 6 of the included publications reported data on 5 RWE studies, all of which studied ocrelizumab (Table 1).

Figure 1. PRISMA Diagram for the Systematic Literature Review



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
[a] The category "Other" includes duplicate references and conference abstracts before 2017.

Figure 2. Mean/Median Percentage Change From Baseline in IgG Levels: Clinical Trials of Ocrelizumab and Ofatumumab



CFB = change from baseline; IgG = immunoglobulin G.
Note: Change in IgG levels are for summary purposes only; owing to heterogeneity in trial designs and outcomes, cross-trial comparisons should not be made. OBOE reported cerebrospinal fluid IgG levels only.
ASCLEPIOS I/ II[1]; ASCLEPIOS I/II, APLIOS, and ALITHIOS[3]; NCT00676715[8]; OBOE[4]; OPERA I/II.[16]

Table 1. Study Design and Outcomes Reported

Trial Name, Author, Country	Study Design and Duration	Treatment (n)	Outcomes Reported: Mean or Median IgA	Mean or Median IgG	Mean or Median IgM	Change From Baseline IgA	Change From Baseline IgG	Change From Baseline IgM	% Achieving a Certain Level IgA	% Achieving a Certain Level IgG	% Achieving a Certain Level IgM
Clinical Trials											
ASCLEPIOS I,[2] multinational	Phase 3 RCT, multicenter, double-blind, 120 weeks	Ofatumumab (n = 465)		✓	✓						
		Teriflunomide (n = 462)									
ASCLEPIOS II,[2] multinational	Phase 3 RCT, multicenter, double-blind, 120 weeks	Ofatumumab (n = 481)		✓	✓						
		Teriflunomide (n = 474)									
ASCLEPIOS I and II pooled	As above	As above		✓	✓		✓[a]	✓[a]		✓	✓
ASCLEPIOS I/II, APLIOS, APOLITOS, ALITHIOS,[3] multinational	ASCLEPIOS I/II (phase 3 RCT), APOLITOS (phase 2 RCT), APLIOS (phase 2 RCT), (long term) ALITHIOS (phase 3, open-label, single-arm, extension study) Results reported up to 3.5 years	ASCLEPIOS I/II: ofatumumab vs. teriflunomide									
		APOLITOS: ofatumumab 20 mg vs. placebo									
		APLIOS: ofatumumab with pre-filled syringe vs. ofatumumab with auto-injector		✓	✓		✓[a]	✓[b]		✓	✓
		ALITHIOS: ofatumumab									
OBOE,[4] multinational NCT02688985	Phase 4, open-label, RCT 52 weeks	Ocrelizumab 600 mg (n = 79 of 100 total people with RMS with available CSF samples)		✓	✓		✓[a]	✓[a]			
VELOCE,[5] US and Canada NCT02545868	Phase 3, open-label, multicenter RCT 24 weeks	Ocrelizumab 600 mg (n = 68)		✓	✓						
		Control (n = 34)									
OPERA I and II pooled,[6] multinational	Phase 3, multicenter, double-blind RCT 96 weeks with 3-year open-label extension	Ocrelizumab (n = 410) (n = 417)	✓	✓	✓	✓[a]	✓[b]	✓[b]	✓	✓	✓
		Interferon beta-1a (n = 411) (n = 418)									
OMS115102,[7] multinational	Phase 2, multicenter, double-blind, crossover, dose-finding RCT 48-week treatment period followed by an individualized treatment period of up to 2 years	Ofatumumab 100 mg to Week 24 then placebo (n = 8)									
		Ofatumumab 300 mg to Week 24 then placebo (n = 11)									
		Ofatumumab 700 mg to Week 24 then placebo (n = 7)				✓	✓	✓			
		Placebo to Week 24 then ofatumumab 100 mg (n = 4)									
		Placebo to Week 24 then ofatumumab 300 mg (n = 4)									
		Placebo to Week 24 then ofatumumab 700 mg (n = 4)									
NCT00676715,[8] multinational	Phase 2, multicenter, double-blind RCT 72-week treatment period followed by an 18-month treatment-free period	Placebo (n = 54)									
		Ocrelizumab 600 mg (n = 55)					✓	✓			
		Ocrelizumab 2,000 mg (n = 55)									
		Interferon beta-1a (n = 54)									
Real-World Evidence											
Prezioso et al.,[9] Italy	Single-arm interventional study; 12 months	Ocrelizumab (n = 42)		✓	✓						
van Lierop et al.,[10] the Netherlands	Observational cohort study; Median follow-up, 21 months	Ocrelizumab direct switch (n = 27)									
		Ocrelizumab indirect switch (n = 15)		✓							
Edgar et al.,[11] US	Retrospective chart review Duration of follow-up NR	Ocrelizumab super responsec (n = 13)									
		Ocrelizumab remaining population (n = 122)		✓	✓						
Evertsson et al.,[12] Evertsson et al.,[13] US	Retrospective cohort study 12 months	Ocrelizumab (n = 161)		✓	✓		✓	✓			
Lopez Ruiz et al.,[14] Spain	Retrospective observational study; Mean follow-up, 19 months	Ocrelizumab (n = 52)		✓	✓					✓	✓

CSF = cerebrospinal fluid, NR = not reported.
[a] Reports % CFB only.
[b] Reports both absolute CFB and % CFB data.
[c] Rapid improvement in symptom profiles, relapse free, and with MRI stability.

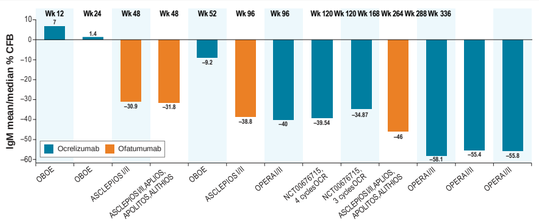
IgG

- Change in IgG was the most reported outcome of all included studies (Figure 2).
- While a transient decrease occurred IgG levels at week 48, 5 trial populations of ofatumumab with 104-168 weeks of follow-up reported that IgG levels did not decrease over time.
- 4 trial populations of ocrelizumab with 24-336 weeks of follow-up reported a decrease in IgG levels over time.
  - The OPERA I and II trials reported a decrease in mean IgG levels over 336 weeks for the ocrelizumab treatment arm, and IgG decreased at a rate of 2.99% per year after the switch to ocrelizumab treatment in the interferon β-1a arm.[16]
  - NCT00676715 reported a mean reduction of 6.94% in IgG level at Week 120 compared with baseline in people who received 4 cycles of ocrelizumab.[8]
- With 52-78 weeks of follow-up, the 5 RWE studies of ocrelizumab generally reported IgG to be stable or to decrease only slightly. Results were variable, and it was often unclear whether any decrease was statistically significant. No RWE studies of ofatumumab were identified.

IgM

- In the same trials that reported IgG, IgM levels decreased over time for both ocrelizumab and ofatumumab (Figure 3).
- The ASCLEPIOS I and II trials reported a mean decrease of 30.9% at Week 48 and 38.8% at Week 96 compared with baseline for people treated with ofatumumab.[15] Similarly, for pooled data from the ASCLEPIOS I and II trials with data from the APOLITOS, APLIOS, and ALITHIOS studies, mean decreases of 31.8% and 46% were observed at Week 48 and Week 168, respectively, compared with baseline.[3] While mean serum IgM declined over time, it remained above the LLN during 3.5 years treatment for the majority of patients.
- The OPERA I and II trials reported a consistent decrease in IgM levels from baseline through Week 336, with a mean relative reduction of 55.8% for all ocrelizumab participants combined.[16] NCT00676715 reported a mean reduction of 34.87% in IgM with 3 cycles of ocrelizumab and 39.54% with 4 cycles of ocrelizumab.[8]
- All 4 RWE studies reporting IgM values also reported a decrease in IgM levels over time with ocrelizumab treatment. No RWE studies of ofatumumab were identified.

Figure 3. Mean/Median Percentage Change From Baseline in IgM Levels: Clinical Trials of Ocrelizumab and Ofatumumab



IgM = immunoglobulin M. Change in IgM levels are for summary purposes only; owing to heterogeneity in trial designs and outcomes, cross-trial comparisons should not be made. OBOE reported cerebrospinal fluid IgG levels only.

IgA

- IgA data were reported in only 2 trial populations.
  - OPERA I/II reported a mean decline of 21.3% at Week 264 compared with baseline for people taking ocrelizumab.[17] At Week 312, 7.5% of those treated with ocrelizumab had IgA below the lower limit of normal (LLN).[16]
  - OMS115102 appeared to show that IgA remained stable for 38 people treated intravenously with 100 mg, 300 mg, or 700 mg of ofatumumab.[7]
- No values were provided for IgA levels in any of the included RWE studies. However, Evertsson et al.[12] reported that levels of IgA in blood were not affected by 12 months of ocrelizumab treatment.

TLR: Association Between Ig Levels and Infection Risk

- Of the 880 articles identified for the TLR, 28 publications relating to 16 studies met the inclusion criteria.
  - Most studies found that IgG levels were a significant predictor of infection in people with MS or that a higher percentage of people with IgG levels below LLN experienced infection compared with people with normal IgGlevels.[18,19]
  - No evidence of a relationship between IgM levels and infections was found.
  - Only one identified study included IgA, and it reported that increased IgA levels were related to reduced infections. [19]
  - In the ASCLEPIOS studies, no association was observed with decreased IgM/IgG levels and increased risk of serious/nonserious infections in ofatumumab-treated patients.[20]
  - Over 288 weeks of ocrelizumab exposure, there was an apparent association between decreased levels of IgG (and less so for IgM or IgA) and serious infections, but overall incidence is low.[21]

LIMITATIONS

As this is a literature review, the methodology does not support cross-study comparisons. Additionally, differences in study designs, populations, sample size, follow-up duration, and definitions of infection should be considered in the interpretation of results. Many of the included publications were conference abstracts/posters and, therefore, reported limited details.

REFERENCES: 1. Nicholas J, et al. Longer-term safety of ofatumumab in patients with relapsing multiple sclerosis. Presented at: Consortium of Multiple Sclerosis Centers Annual Meeting 2022; June 1-4, 2022; National Harbor, MD. **2.** Hauser SL, N Engl J Med. 2020;383(6):546-57. **3.** Wiendl H, et al. Effect of ofatumumab on serum immunoglobulin levels and infection risk in patients with relapsing multiple sclerosis over 3.5 years. ECTRIMS 2021; 13-15 October 2021. **4.** Weber M, et al. Mult Scler. 2020;26(3 SUPPL):171-2. **5.** Bar-Or A, et al. Neurology. 2020;95(14):e1999-e2008. **6.** Hauser SL, et al. N Engl J Med. 2017;376(3):221-34. **7.** NCT. 2010. https://ClinicalTrials.gov/show/NCT00640328. **8.** Baker D, et al. Mult Scler Relat Disord. 2020;44. **9.** Prezioso C, et al. Viruses. 2021;13(9). **10.** van Lierop ZYGJ, et al. Mult Scler J Exp Transl Clin. 2020;6(4). **11.** Edgar N, et al. Mult Scler. 2020;26(3 SUPPL):267. **12.** Evertsson B, et al. Mult Scler J Exp Transl Clin. 2020;6(4). **13.** Evertsson B, et al. Mult Scler. 2019;25:515-6. **14.** Lopez Ruiz R, et al. Real world data on the use of ocrelizumab. Incidence of lymphopenia, B-cell and immunoglobulins evolution. ECTRIMS 2021 13-15 October 2021. **15.** European Medicines Agency. https://www.ema.europa.eu/en/documents/assessment-report/kesimpta-epar-public-assessment-report_en.pdf. **16.** Hauser SL, et al. Neurology. 2021 Sep 2. **17.** Derfuss T, et al. Clin Neurophysiol. 2020;131(4):e196. **18.** Disanto G, et al. Mult Scler J. 2021;27(8):1230-9. **19.** Séery N, et al. CNS Drugs. 2021;35(8):907-18. **20.** Wiendl H, et al. Mult Scler J. 2020;26(3 SUPPL):233-4. **21.** Derfuss T, Weber MS, et al. Mult Scler. 2019;25:20-1.