Effect of Ocrelizumab on Humoral Immunity Markers in the Phase III, Double-Blind, Double-Dummy, Interferon β-1a–controlled OPERA I and OPERA II Studies

A Bar-Or,[1] DL Arnold,[1,2] G Comi,[3] HP Hartung,[4] SL Hauser,[5] F Lublin,[6] K Selmaj,[7] A Traboulsee,[8] G Klingelschmitt,[9] C Marcillat,[9] J Napieralski,[9] L Kappos[10] on behalf of the OPERA I and OPERA II investigators

[1]McGill University, Montreal, QC, Canada; [2]NeuroRx Research, Montreal, QC, Canada; [3]University Vita-Salute San Raffaele, Milan, Italy; [4]Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; [5]University of California, San Francisco, CA, USA; [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Medical University of Lodz, Lodz, Poland; [8]University of British Columbia, Vancouver, BC, Canada; [9]F. Hoffmann La-Roche Ltd, Basel, Switzerland; [10]University Hospital Basel, Basel, Switzerland

BACKGROUND

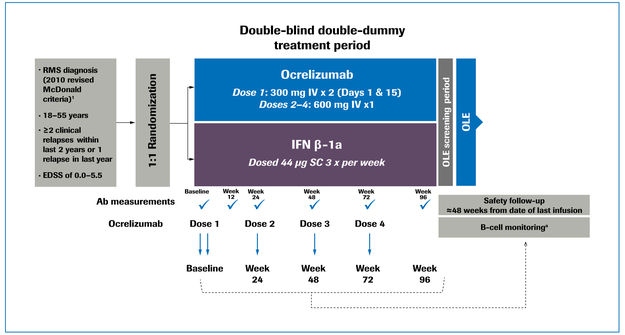
- Ocrelizumab (OCR) is a humanized monoclonal antibody that targets CD20$^+$ B cells; selective depletion of CD20$^+$ B cells may potentially preserve the capacity for B-cell reconstitution and pre-existing humoral immunity (acquired immune response)
- OPERA I and OPERA II were two identical Phase III, randomized, double-blind, double-dummy, active-controlled trials to evaluate the efficacy and safety of OCR vs IFN β-1a in patients with relapsing MS (RMS)
- The objective of this investigation was to assess the effect of OCR on specific humoral immunity in patients with RMS from the OPERA I and OPERA II studies

METHODS

Study Design

- Patients were randomized (1:1) to receive OCR 600 mg via intravenous infusion every 24 weeks or subcutaneous IFN β-1a 44 µg three times weekly through a 96-week treatment period (**Figure 1**)

Figure 1. OPERA I and OPERA II study design



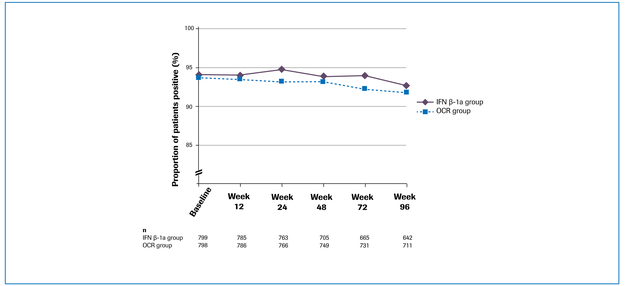
*Continued monitoring occurs if B cells are not repleted.
Ab, antibody; EDSS, Expanded Disability Status Scale; IFN, interferon; IV, intravenous; OLE, open-label extension; RMS, relapsing multiple sclerosis; SC, subcutaneous.

- Patients in both groups received corresponding subcutaneous or intravenous placebo treatments
- All patients received intravenous methylprednisolone 100 mg (and optional analgesics/antipyretics and antihistamines) prior to infusion
- Eligible patients were stratified by region (USA vs rest of world) and baseline Expanded Disability Status Scale score (<4.0 vs ≥4.0)
- Prior to study enrolment, physicians were advised to review patient immunization status and follow local guidance for vaccination; immunizations were to be completed ≥6 weeks prior to treatment
- Measurements of antibody (Ab) titers against mumps virus, rubella virus, varicella zoster virus, and *Streptococcus pneumoniae* were taken at baseline and at weeks 12, 24, 48, 72, and 96

RESULTS

- The pooled safety analysis of the OPERA I and OPERA II studies included 826 IFN β-1a–treated and 825 OCR-treated patients
- The proportion of patients with positive levels of Ab against mumps virus at baseline was 94.1% and 93.6% in the IFN β-1a and OCR groups, respectively; this proportion ranged (min-max) 92.7–94.8% and 91.8–93.5% over the 96-week study treatment period (**Figure 2**)

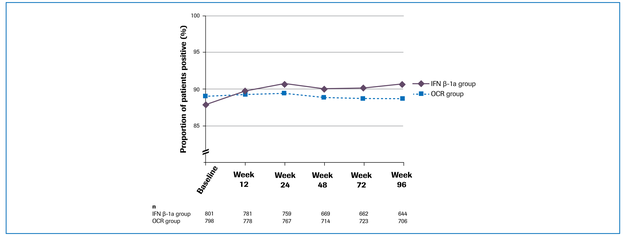
Figure 2. The proportion of patients with positive levels of Ab against mumps virus over the 96-week treatment period



Ab, antibody; IFN, interferon; OCR, ocrelizumab.

- The proportion of patients with positive levels of Ab against rubella virus at baseline was 87.9% and 89.0% in the IFN β-1a and OCR groups, respectively; this proportion ranged (min-max) 89.8–90.8% and 88.7–89.4% over the treatment period (**Figure 3**)

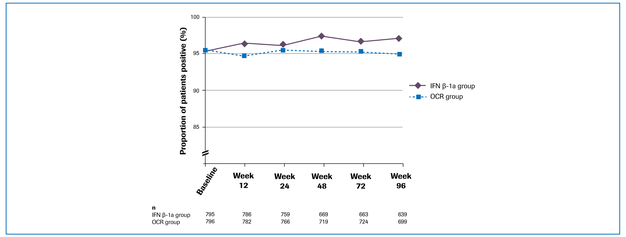
Figure 3. The proportion of patients with positive levels of Ab against rubella virus over the 96-week treatment period



Ab, antibody; IFN, interferon; OCR, ocrelizumab.

- The proportion of patients with positive levels of Ab against varicella zoster virus was 95.5% in both treatment groups; this proportion ranged (min-max) 96.2–97.5% and 94.8–95.6% over the treatment period in the IFN β-1a and OCR treatment groups, respectively (**Figure 4**)

Figure 4. The proportion of patients with positive levels of Ab against varicella zoster virus over the 96-week treatment period



Ab, antibody; IFN, interferon; OCR, ocrelizumab.

- Among evaluable patients, the mean (SD) level of Ab against *S. pneumoniae* at baseline was 53.67 (54.13) mg/L and 55.35 (67.00) mg/L in the IFN β-1a and OCR groups, respectively (**Table 1**)
- At Week 96, the mean change from baseline was -1.13 (40.25) mg/L and -1.99 (59.60) mg/L in the IFN β-1a and OCR groups, respectively

Table 1. The level of Ab against *Streptococcus pneumoniae* capsular polysaccharide in evaluable patients over the 96-week treatment period

Visit	IFN β-1a n=826		OCR n=825	
	Value at visit (mg/L)	Change from baseline (mg/L)	Value at visit (mg/L)	Change from baseline (mg/L)
Baseline				
n	796	–	785	–
Mean (SD)	53.67 (54.13)	–	55.35 (67.00)	–
Median	40.05	–	40.80	–
Min–max	6.4–657.3	–	5.7–856.6	–
Week 12				
n	781	755	778	747
Mean (SD)	53.54 (54.66)	-0.13 (42.58)	59.63 (80.34)	3.52 (40.52)
Median	40.50	-0.40	42.25	1.10
Min–max	5.9–842.0	-422.4–809.3	5.7–1280.4	-240.8–887.9
Week 24				
n	753	730	766	734
Mean (SD)	55.47 (64.09)	1.76 (48.66)	57.90 (73.84)	1.17 (45.16)
Median	40.70	-0.05	41.05	1.10
Min–max	6.1–1154.8	-240.8–1122.1	5.5–1330.1	-387.9–937.6
Week 48				
n	700	675	744	712
Mean (SD)	55.04 (63.39)	1.37 (55.06)	55.23 (70.10)	-0.43 (46.39)
Median	39.90	-1.00	40.05	-0.40
Min–max	6.0–796.3	-342.3–753.3	5.9–1290.4	-317.5–897.9
Week 72				
n	663	640	727	694
Mean (SD)	52.81 (49.14)	-1.27 (44.82)	54.70 (59.80)	-0.50 (44.44)
Median	39.40	-0.80	40.20	-0.55
Min–max	6.2–668.7	-359.1–636.0	5.6–1267.6	-289.5–875.1
Week 96				
n	642	618	709	678
Mean (SD)	51.74 (42.50)	-1.13 (40.25)	54.06 (80.98)	-1.99 (59.60)
Median	39.50	-1.05	39.60	-1.60
Min–max	5.6–487.1	-358.6–469.0	5.5–1303.2	-427.7–971.9

CONCLUSIONS

- **Ocrelizumab did not appear to have an effect on specific humoral immunity (Ab titers) to common bacterial viral antigens (mumps virus, rubella virus, varicella zoster virus and *S. pneumoniae*) during the controlled treatment periods of the RMS studies**
- **Formal assessment of the impact of ocrelizumab on immunization response has not been completed to date**

DISCLOSURES

A Bar-Or has served on scientific advisory boards for F Hoffmann-La Roche Ltd, Genentech, Biogen Idec, GlaxoSmithKline, Merck/EMD Serono, Medimmune, Mitsubishi Pharma, Ono Pharma, Receptos, Sanofi–Genzyme, and Guthy-Jackson/GGF; he has also received research support from Novartis and Sanofi–Genzyme; DL Arnold reports equity interest in NeuroRx Research, which performed the MRI analysis for the trial, and consultation fees from Acorda, Biogen Idec, Genzyme, F Hoffmann-La Roche Ltd, Innate Immunotherapeutics, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Sanofi Aventis, and Teva; G Comi has received compensation for consulting services and/or speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Bayer, Excemed, Serono Symposia International Foundation, Almirall, Chugai, Receptos, Hans-Peter Hartung has received fees for consulting, serving on steering committees and ad boards, and speaking at scientific symposia from Biogen, F Hoffmann-La Roche Ltd, GeNeuro, Genzyme, Merck Serono, Novartis, Octapharma, Opexa, Receptos, Sanofi, and Teva with approval by the Rector of Heinrich-Heine-University; SL Hauser serves on the scientific advisory boards for Annexon, Symbiotix, Bionure; he has also received travel reimbursement and writing assistance from F Hoffman-La Roche Ltd for CD20-related meetings and presentations; F Lublin reports funding of research from Biogen Idec, Novartis Pharmaceuticals Corp,Teva Neuroscience, Inc., Genzyme, Sanofi, Celgene, Transparency Life Sciences, NIH, NMSS; consulting agreements/advisory boards/DSMB for Bayer HealthCare Pharmaceuticals, Biogen Idec, EMD Serono, Inc., Novartis,Teva Neuroscience, Actelion, Sanofi, Acorda, Questcor/Mallinckrodt, F Hoffmann-La Roche Ltd, Genentech, Celgene, Genzyme, MedImmune, Osmotica, Xenoport, Receptos, Forward Pharma, BBB technologies, Akros; is co-chief editor for Multiple Sclerosis and Related Diseases; and has current financial interests/stock ownership in Cognition Pharmaceuticals, Inc.; K Selmaj has received honoraria for advisory boards from Biogen, Novartis, Teva, F Hoffmann-La Roche Ltd, Merck, Synthon, Receptos, Genzyme. A Traboulsee has received speaker fees and/or advisory board fees from Biogen, F Hoffmann-La Roche Ltd, Genzyme, Serono, and Teva; and clinical trial and/or grant support from Biogen, Chugai, Canadian Institute for Health Research, Genzyme, F Hoffman.-La Roche Ltd, Michael Smith Foundation, and the MS Society of Canada; G Klingelschmitt, C Marcillat and J Napieralski are employees and/or shareholders of F Hoffmann-La Roche Ltd; L Kappos reports that his institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee, advisory board, and consultancy fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, and Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi, and Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva; royalties from Neurostatus Systems AG; and grants from Bayer HealthCare, Biogen, F Hoffmann-La Roche Ltd, Merck, Novartis, the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation, the European Union, and Roche Research Foundations.

ACKNOWLEDGMENTS

We would like to thank all patients, their families and the investigators who participated in this trial. We would also like to thank P Chin, P Fontoura, H Garren and D Masterman for their input in the development of this poster. This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Support for third-party writing assistance for this presentation was provided by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

REFERENCE

1. Polman C, *et al. Ann Neurol* 2011;69:292–302.