Infusion-Related Reactions With Ocrelizumab in the Phase III Double-Blind, Double-Dummy, Interferon β-1a–Controlled OPERA I and OPERA II Studies

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

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

BACKGROUND

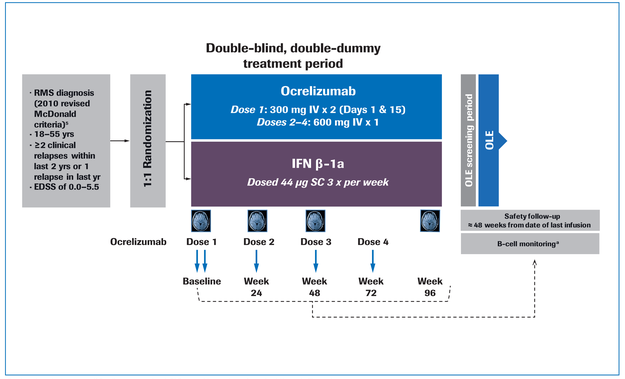
- Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively depletes CD20+ B cells[1]
- Infusion-related reactions (IRRs) have been observed with the administration of drugs, including monoclonal antibodies such as OCR[2,3]
- IRRs typically occur during or a few hours post-infusion, although symptoms may be delayed for up to 24 hours and may vary in severity[4]
- OPERA I and OPERA II were two identical randomized, double-blind, double-dummy, Phase III trials to evaluate the efficacy and safety of OCR vs interferon (IFN) β-1a in patients with relapsing multiple sclerosis (RMS)
- The incidence of IRRs was assessed in patients with RMS in a pooled safety analysis of OPERA I and OPERA II

METHODS

Study Design

- Patients were randomized (1:1) to receive OCR 600 mg via intravenous (IV) infusion every 24 weeks or subcutaneous (SC) IFN β-1a 44 µg three times weekly through a 96-week treatment period (**Figure 1**)
- Patients in both groups received corresponding SC or IV placebo treatments
- Eligible patients were stratified by region (USA vs rest of world) and baseline Expanded Disability Status Scale (EDSS) score (<4.0 vs ≥4.0)

Figure 1. OPERA study design



*Continued monitoring occurs if B cells are not repleted. OLE to provide ongoing safety, tolerability and efficacy data.
EDSS, Expanded Disability Status Scale; IFN, interferon; IV, intravenous; OLE, open-label extension; RMS, relapsing multiple sclerosis; SC, subcutaneous.

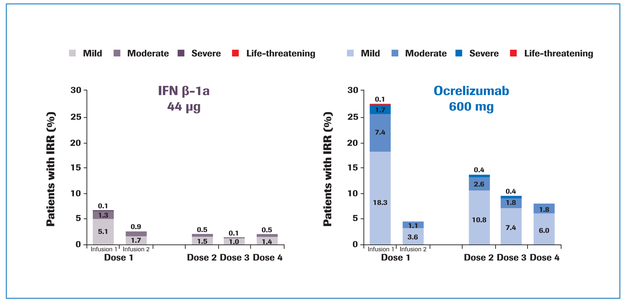
Prophylactic Management and Monitoring of IRRs

- IRRs were defined as adverse events (e.g. "rash") that occurred during or within 24 hours of IV infusion of OCR or placebo
- IRRs were categorized by the time of occurrence as follows:
  - During the infusion
  - One hour post-infusion, while the patient was in the clinic
  - Within 24 hours of completion of the infusion and the patient was not in the clinic
- To reduce the incidence of potential IRRs, all patients received prophylactic treatment with methylprednisolone (100 mg), administered by slow IV infusion and completed 30 minutes before the start of each OCR or placebo infusion
- Optional prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) and/or an IV or oral antihistaminic such as IV diphenhydramine (50 mg) or its equivalent, 30–60 minutes before the start of an infusion, was offered to all patients
- IRRs were to be treated symptomatically with oral acetaminophen/paracetamol (1 g) and intramuscular or slow IV antihistamines such as diphenhydramine (25–100 mg); non-allergic events were to be treated symptomatically as judged clinically relevant by the Investigator

RESULTS

- In pooled analysis of OPERA I and OPERA II, the proportion of patients with at least one IRR during the 96-week treatment period was 9.7% (n=80) in the IFN β-1a group and 34.3% (n=283) in the OCR group
  - In OPERA I, 7.3% (n=30) of patients in the IFN β-1a group vs 30.9% (n=126) of patients in the OCR group reported at least one IRR
  - In OPERA II, 12.0% (n=50) of patients in the IFN β-1a group vs 37.6% (n=157) of patients in the OCR group reported at least one IRR
- Incidence of IRRs in the OCR group was highest with the first infusion (Dose 1, Day 1: 27.5% [n=227]) and decreased with subsequent doses (Dose 1, Day 15: 4.7% [n=38]; Dose 2: 13.7% [n=107]; Dose 3: 9.6% [n=73]; Dose 4: 7.8% [n=57]; **Figure 2**)
  - In OPERA I, 63.3% (n=19) of patients reporting an IRR at anytime in the IFN β-1a group reported an IRR with the first infusion of Dose 1 vs 82.5% (n=104) in the OCR group
  - In OPERA II, 70.0% (n=35) of patients reporting an IRR at anytime in the IFN β-1a group reported an IRR with the first infusion of Dose 1 vs 78.3% (n=123) in the OCR group
- The majority of IRRs were mild to moderate in severity (IFN β-1a: 98.8% [n=79] vs OCR: 92.6% [n=262]; **Figure 2**)
  - In OPERA I, 100% (n=30) of patients reporting at least one IRR in the IFN β-1a group vs 88.1% (n=111) in the OCR group reported IRRs of mild to moderate severity
  - In OPERA II, 98.0% (n=49) of patients reporting at least one IRR in the IFN β-1a group vs 96.2% (n=151) in the OCR group reported IRRs of mild to moderate severity
- Severe IRRs were reported by 0.1% (n=1) of patients in the IFN β-1a group and 2.4% (n=20) of patients in the OCR group (**Figure 2**)
  - In the OCR group, incidence of severe IRRs was highest with the first infusion (Dose 1, Day 1: 1.7% [n=14]) and decreased with subsequent doses (Dose 1, Day 15: 0; Dose 2: 0.4% [n=3]; Dose 3: 0.4% [n=3]; Dose 4: 0)
  - In OPERA I, there were no patients that reported severe IRRs in the IFN β-1a group vs 3.4% (n=14) of patients in the OCR group
  - In OPERA II, 0.2% (n=1) vs 1.4% (n=6) of patients reported severe IRRs in the IFN β-1a and OCR groups, respectively
- In OPERA I, 0.1% (n=1) of patients in the OCR group had a life-threatening IRR (bronchospasm) during the first infusion; the patient was withdrawn per protocol
- There were no fatal IRRs reported in OPERA I and OPERA II

Figure 2. Percentage of patients with ≥1 IRR in OPERA I and OPERA II by dose and severity



Numbers in columns represent the proportion of patients experiencing a grade of IRR.
IFN, interferon; IRR, infusion-related reaction.

- The most frequent (≥5%) IRR symptoms in the OCR group were pruritus, rash, throat irritation and flushing (**Table 1**)

Table 1. Most frequent (≥5%) IRRs over 96 weeks in OPERA I and OPERA II

n (%)	IFN β-1a 44 µg N=826	OCR 600 mg N=825
Total number of patients with IRRs	**80 (9.7)**	**283 (34.3)**
Pruritis	6 (7.5)	85 (30.0)
Rash	2 (2.5)	85 (30.0)
Throat irritation	1 (1.3)	67 (23.7)
Flushing	9 (11.3)	45 (15.9)
Headache	14 (17.5)	27 (9.5)
Urticaria	0	25 (8.8)
Oropharyngeal pain	0	24 (8.5)
Tachycardia	14 (17.5)	13 (4.6)
Pyrexia	11 (13.8)	12 (4.2)
Nausea	13 (16.3)	10 (3.5)
Hypotension	6 (7.5)	9 (3.2)
Myalgia	5 (6.3)	8 (2.8)
Dizziness	5 (6.3)	6 (2.1)

Percentages of total number of patients with IRRs are based on N.
Percentages of number of patients with symptoms are based on total number of patients who had IRRs.
IFN, interferon; IRR, infusion-related reaction; OCR, ocrelizumab.

- In the OCR group, the majority of IRRs, including severe IRRs, were reported during infusion and decreased in incidence one hour post-infusion (while patients were in the clinic) and 24 hours post-infusion (while patients were not in the clinic; **Table 2**)
  - The incidence of IRRs during infusion was highest with the administration of the first infusion of Dose 1 and decreased with subsequent infusions

Table 2. Percentage of patients with ≥1 IRR by time of event and by dose and severity in OPERA I and OPERA II

n (%)	Mild		Moderate		Severe		Life-threatening	
	IFN β-1a 44 µg	OCR 600 mg	IFN β-1a 44 µg	OCR 600 mg	IFN β-1a 44 µg	OCR 600 mg	IFN β-1a 44 µg	OCR 600 mg
During infusion								
Dose 1, Infusion 1	16 (1.9)	120 (14.5)	6 (0.7)	47 (5.7)	0	14 (1.7)	0	1 (0.1)
Dose 1, Infusion 2	8 (1.0)	17 (2.1)	0	4 (0.5)	0	0	0	0
Dose 2	10 (1.3)	67 (8.6)	2 (0.3)	16 (2.1)	0	1 (0.1)	0	0
Dose 3	4 (0.6)	49 (6.5)	1 (0.1)	13 (1.7)	0	1 (0.1)	0	0
Dose 4	6 (0.9)	36 (4.9)	1 (0.2)	10 (1.4)	0	0	0	0
One hour post-infusion (while patients were in the clinic)								
Dose 1, Infusion 1	9 (1.1)	15 (1.8)	2 (0.2)	5 (0.6)	1 (0.1)	0	0	0
Dose 1, Infusion 2	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	0	0	0	0
Dose 2	0	5 (0.6)	0	1 (0.1)	0	1 (0.1)	0	0
Dose 3	0	2 (0.3)	0	1 (0.1)	0	1 (0.1)	0	0
Dose 4	2 (0.3)	2 (0.3)	0	2 (0.3)	0	0	0	0
Within 24 hours post-infusion (while patients were not in the clinic)								
Dose 1, Infusion 1	17 (2.1)	17 (2.1)	3 (0.4)	9 (1.1)	0	0	0	0
Dose 1, Infusion 2	4 (0.5)	10 (1.2)	5 (0.6)	3 (0.4)	0	0	0	0
Dose 2	1 (0.1)	13 (1.7)	2 (0.3)	3 (0.4)	0	1 (0.1)	0	0
Dose 3	3 (0.4)	5 (0.7)	0	0	0	1 (0.1)	0	0
Dose 4	1 (0.2)	6 (0.8)	2 (0.3)	1 (0.1)	0	0	0	0

For total patients with at least one IRR, percentages are based on number of patients that received the infusion.
For summaries by grade, multiple events in one individual are counted only once (AE with most extreme intensity is used).
AE, adverse event; IFN, interferon; IRR, infusion-related reaction; OCR, ocrelizumab.

- Premedication was recommended to lower the incidence and severity of IRRs; most IRRs were generally manageable with infusion adjustments and symptomatic treatment
  - In the OCR group, the incidence of IRRs after the first infusion was highest in the premedication subgroup that received methylprednisolone alone (49.5% [n=48]) compared with the subgroups that received methylprednisolone plus analgesics/antipyretics (32.7% [n=18]), methylprednisolone plus antihistaminics (19.2% [n=23]) and methylprednisolone plus analgesics/antipyretics and antihistaminics (24.9% [n=137])
  - A total of 22.4% (n=185) of patients in the OCR group (OPERA I: 22.1% [n=90]; OPERA II: 22.8% [n=95]) and 4.1% (n=34) of patients in IFN β-1a group (OPERA I: 3.2% [n=13]; OPERA II: 5.0% [n=21]) received at least one concomitant treatment for IRRs during the 96-week treatment period
  - The addition of antihistaminics with methylprednisolone as premedication appeared to decrease the incidence of IRRs
- During the overall treatment period, 1.3% (n=11) of patients (OPERA I: 1.5% [n=6]; OPERA II: 1.2% [n=5]) withdrew from the OCR group due to an IRR, all of which were reported at the first infusion
  - The most frequent (>10%) IRR symptoms reported by the 11 patients who withdrew from treatment were rash, pruritis, throat irritation, dyspnea, nasal congestion and flushing

CONCLUSIONS

- **In OPERA I and OPERA II, the most common adverse events were IRRs; IRRs were mostly mild to moderate in severity and were generally manageable**
- **IRRs with ocrelizumab administration were most frequent with the first infusion and decreased in incidence and severity with subsequent doses**

DISCLOSURES

K Selmaj has received honoraria for advisory boards from Biogen, Novartis, Teva, F. Hoffmann-La Roche Ltd, Merck, Synthon, Receptos and Genzyme; D Arnold reports equity interest in NeuroRx Research, which performed the MRI analysis for the trial, and consultation fees from Acorda Therapeutics, Biogen, Genzyme, F. Hoffmann-La Roche Ltd, Innate Immunotherapeutics, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Sanofi and Teva; 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/GDF; he has also received research support from Novartis and Sanofi-Genzyme; 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 and Receptos; HP Hartung has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine-University from Bayer, Biogen, GeNeuro, Genzyme, Merck Serono, MedImmune, Novartis, Octapharma, Opexa, F. Hoffmann-La Roche Ltd, Teva and Sanofi; SL Hauser serves on the scientific advisory boards for Annexon, Symbiotix and Bionure; he has also received travel reimbursement and writing assistance from F. Hoffmann-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 and 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, Inc., Celgene, Genzyme, MedImmune, Osmotica, Xenoport, Receptos, Forward Pharma, BBB technologies and Akros; is co-chief editor for Multiple Sclerosis and Related Diseases; and has current financial interests/stock ownership in Cognition Pharmaceuticals, Inc.; A Traboulsee has received honoraria for advisory boards from Genzyme F. Hoffmann-La Roche Ltd. He is a steering committee member for F. Hoffmann-La Roche Ltd; N Mairon, G Klingelschmitt and J Napieralski are employees and/or shareholders of F. Hoffmann-La Roche Ltd; L Kappos's institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof Kappos' activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Addex, Almirall, Bayer Health Care Pharmaceuticals, CLC Behring, Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharma, Pfizer, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Siemens, Teva, UCB and Xenport; royalties from Neurostatus AG; research grants from the Swiss MS Society, Swiss National Research Foundation, the European Union, Gianni Rubatto Foundation and the Novartis Research Foundation and Roche Research Foundation.

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REFERENCES

1. Kappos L, *et al. Lancet* 2011;378(9805):1779–1787.
2. Phillips JT, *et al. Neurology* 2008;67(9):1717–1718.
3. Caon C, *et al. Int J MS Care* 2015;17(4):191–198.
4. Lenz HJ, *Oncologist* 2007;12(5):601–609.
5. Polman C, *et al. Ann Neurol* 2011;69:292–302.

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