Infusion-Related Reactions in the Phase III Double-Blind, Placebo-Controlled ORATORIO Study of Ocrelizumab in Primary Progressive Multiple Sclerosis

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BACKGROUND

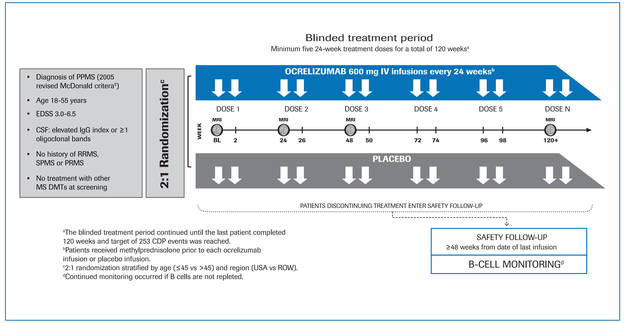
- Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively depletes CD20$^+$ B cells[1]
- Infusion-related reactions (IRRs) have been observed with the administration of drugs, including monoclonal antibodies such as OCR[2,3]
- IRRs typically occur during or a few hours post-infusion, although symptoms may be delayed for up to 24 hours and may vary in severity[4]
- ORATORIO was a randomized, double-blind, placebo (PBO)-controlled, Phase III study to evaluate the efficacy and safety of OCR in patients with primary progressive multiple sclerosis (PPMS)
- The incidence of IRRs in patients with PPMS enrolled in ORATORIO was assessed in a safety analysis

METHODS

Study Design

- Patients were randomized (2:1) to receive OCR 600 mg, given as two 300-mg intravenous (IV) infusions 14 days apart, or corresponding PBO every 24 weeks for ≥120 weeks until an overall prespecified number of 12-week confirmed disability progression (CDP) events occurred (**Figure 1**)
- The double-blind treatment period was designed to end when approximately 253 CDP events were reached, based on the original sample size assumptions
- If the number of events had not been reached 120 weeks after the last patient was randomized, the study would continue until the target number of events had been reached
- Eligible patients were stratified by age (≤45 vs >45 years) and region (USA vs rest of world)
- Patients discontinuing treatment entered safety follow-up for ≥48 weeks from the date of the last infusion followed by B-cell monitoring if B cells were not repleted

Figure 1. ORATORIO study design



[a]The blinded treatment period continued until the last patient completed 120 weeks and target of 253 CDP events was reached.
[b]Patients received methylprednisolone prior to each ocrelizumab infusion or placebo infusion.
[c]2:1 randomization stratified by age (≤45 vs >45) and region (USA vs ROW).
[d]Continued monitoring occurred if B cells are not repleted.

BL, baseline; CDP confirmed disability progression; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IV, intravenous; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

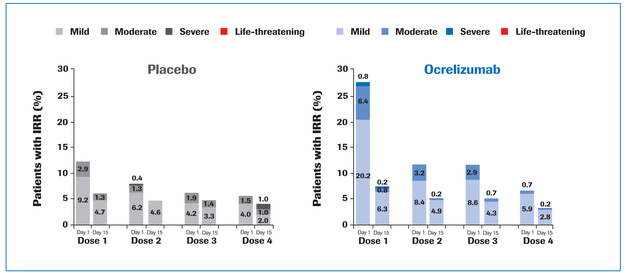
Prophylactic Management and Monitoring of IRRs

- IRRs were defined as adverse events (AE) that occurred during or within 24 hours of IV infusion of OCR or PBO
- 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 infusion
- Optional prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) and 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 ORATORIO, the proportion of patients with at least one IRR during the controlled treatment period was 25.5% (n=61) in the PBO group and 39.9% (n=194) in the OCR group
- Among the total number of patients with at least one IRR, the highest incidence of IRRs was associated with the first infusion in both treatment groups (PBO: 47.5% [n=29]; OCR: 68.6% [n=133]) and decreased with subsequent doses (**Figure 2**)
  - — A greater proportion of patients in each group experienced IRRs with the first infusion of each dose compared with the second infusion of that dose
- The majority of IRRs were mild to moderate in severity (PBO: 93.4% [n=57] vs OCR: 96.9% [n=188]; **Figure 2**)
- Severe IRRs were reported by 1.7% (n=4) of patients in the PBO group and 1.2% (n=6) of patients in the OCR group; there were no life-threatening IRRs reported in the ORATORIO study (**Figure 2**)

Figure 2. Percentage of patients with ≥1 IRR in ORATORIO by dose and severity



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

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

Table 1. Most frequent (≥5%) IRR symptoms in ORATORIO

n (%)	Placebo n=239	OCR n=486
Total number of patients with IRRs	**61 (25.5)**	**194 (39.9)**
Pruritis	2 (3.3)	56 (28.9)
Flushing	10 (16.4)	46 (23.7)
Rash	1(1.6)	40 (20.6)
Headache	21 (34.4)	31 (16.0)
Pyrexia	4 (6.6)	26 (13.4)
Throat irritation	1 (1.6)	26 (13.4)
Fatigue	9 (14.8)	17 (8.8)
Nausea	10 (16.4)	16 (8.2)
Oropharyngeal pain	1 (1.6)	15 (7.7)
Dizziness	7 (11.5)	13 (6.7)
Tachycardia	3 (4.9)	12 (6.2)
Urticaria	2 (3.3)	10 (5.2)
Hypertension	4 (6.6)	8 (4.1)
Hypotension	6 (9.8)	7 (3.6)
Asthenia	4 (6.6)	4 (2.1)
Somnolence	4 (6.6)	3 (1.5)

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.
IRR, infusion-related reaction; OCR, ocrelizumab.

- Of the patients with ≥1 IRR, a higher proportion in the OCR group reported their onset during the infusion compared with the PBO group; however, the proportion of patients with ≥1 IRR within 24 hours after the end of the infusion, when patients had left the clinic, was higher in the PBO group
  - — The proportion of patients with ≥1 IRR during infusion, one hour post-infusion (while patients were in the clinic) and 24 hours post-infusion (while patients were not in the clinic) by dose and severity is shown up to Dose 3 in **Table 2**; the incidence of IRRs followed a similar trend for the remaining doses in the controlled treatment period

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

	Mild		Moderate		Severe		Life-threatening	
n (%)	Placebo	OCR	Placebo	OCR	Placebo	OCR	Placebo	OCR
During infusion								
Dose 1, Day 1	7 (2.9)	60 (12.3)	1 (0.4)	27 (5.6)	0	4 (0.8)	0	0
Dose 1, Day 15	3 (1.3)	13 (2.7)	1 (0.4)	0	0	0	0	0
Dose 2, Day 1	2 (0.9)	26 (5.6)	1 (0.4)	8 (1.7)	0	0	0	0
Dose 2, Day 15	2 (0.9)	13 (2.9)	0	0	0	0	0	0
Dose 3, Day 1	4 (1.9)	25 (5.5)	1 (0.5)	6 (1.3)	0	0	0	0
Dose 3, Day 15	3 (1.4)	7 (1.6)	1 (0.5)	1 (0.2)	0	0	0	0
One hour post-infusion (while patients were in the clinic)								
Dose 1, Day 1	1 (0.4)	12 (2.5)	0	1 (0.2)	0	0	0	0
Dose 1, Day 15	2 (0.9)	8 (1.7)	0	1 (0.2)	0	0	0	0
Dose 2, Day 1	4 (1.8)	4 (0.9)	1 (0.4)	2 (0.4)	0	0	0	0
Dose 2, Day 15	1 (0.5)	6 (1.3)	0	0	0	0	0	0
Dose 3, Day 1	2 (0.9)	2 (0.4)	0	3 (0.7)	0	0	0	0
Dose 3, Day 15	1 (0.5)	4 (0.9)	0	0	0	0	0	0
Within 24 hours post-infusion (while patients were not in the clinic)								
Dose 1, Day 1	14 (5.9)	25 (5.1)	6 (2.5)	3 (0.6)	0	0	0	0
Dose 1, Day 15	6 (2.6)	8 (1.7)	2 (0.9)	3 (0.6)	0	1 (0.2)	0	0
Dose 2, Day 1	8 (3.5)	9 (1.9)	1 (0.4)	5 (1.1)	1 (0.4)	0	0	0
Dose 2, Day 15	7 (3.2)	3 (0.7)	0	1 (0.2)	0	0	0	0
Dose 3, Day 1	3 (1.4)	11 (2.4)	3 (1.4)	4 (0.9)	0	0	0	0
Dose 3, Day 15	3 (1.4)	8 (1.8)	2 (1.0)	2 (0.5)	0	0	0	0

Percentages by infusion are based on the number of patients who received that infusion.
Multiple occurrences of an IRR in one patient are counted once at the highest grade.
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 (49.2% [n=29]) compared with the subgroups that received methylprednisolone plus analgesics/antipyretics (42.9% [n=9]), methylprednisolone plus antihistaminics (16.7% [n=4]) and methylprednisolone plus analgesics/antipyretics and antihistaminics (23.8% [n=91])
  - — The addition of antihistaminics with methylprednisolone as premedication appeared to decrease the incidence of IRRs
  - — A total of 18.9% (n=92) of patients in the OCR group and 7.5% (n=18) of patients in the PBO group received at least one concomitant treatment for IRRs during the controlled treatment period
- Over the controlled treatment period, a total of 0.4% (n=1) of patients in the PBO group and 0.4% (n=2) in the OCR group withdrew from treatment due to an IRR
- In the OCR group, 0.2% (n=1) of patients withdrew from treatment at first infusion due to an IRR

CONCLUSIONS

- **In ORATORIO, IRRs were mostly mild to moderate in severity and were generally manageable**
- **IRRs were the most common AE in the ocrelizumab group, and among the most frequent AEs in the PBO group**
- **IRRs with ocrelizumab administration were most frequent with the first infusion and decreased in incidence and severity with subsequent doses**

DISCLOSURES

X Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos; DL 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/GGF; he has also received research support from Novartis and Sanofi-Genzyme; J de Seze has received consultancy fees and served as an expert for advisory boards for Alexion, Allergan, Almiral, Bayer, Biogen, Chugai, CSL Behring, F Hoffmann-La Roche Ltd, Genzyme, LFB, Merck, Novartis and Teva; G Giovannoni has received honoraria from AbbVie, Bayer HealthCare, Biogen, Canbex Therapeutics, Five Prime Therapeutics, Genzyme, GSK, GW Pharma, Merck, Merck Serono, Novartis, Protein Discovery Laboratories, F Hoffmann-La Roche Ltd, Synthon, Teva Neuroscience, UCB and Vertex; research grant support from Biogen, Ironwood, Merck Serono, Merz and Novartis; and compensation from Elsevier; B Hemmer has served on scientific advisory boards for F Hoffmann-La Roche Ltd, Novartis, Bayer Schering and Genentech; has received speaker honoraria from Biogen Idec and F Hoffmann-La Roche Ltd; has received research support from Chugai Pharmaceuticals; and holds part of a patent for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and genetic determinants of neutralising antibodies to interferon-beta; K Rammohan has received honoraria for participating in advisory boards and consulting for Acorda, Biogen, EMD Serono, Genentech, Inc./F Hoffmann-La Roche Ltd, Genzyme and Teva; he has also received grants from Accera, Novartis and the United States Department of Defense; N Mairon, J Napieralski and A Sauter are employees and/or shareholders of F Hoffmann-La Roche Ltd; J Wolinsky has served on advisory boards, data monitoring or steering committees, held consulting agreements or received speaker honoraria from the following commercial entities: AbbVie, AcademicCME, Alkermes, Antisense Therapeutics, Bayer HealthCare, Forward Pharma A/S, MedDay, Mapi Scientific, Novartis, Roche/Genentech, Sanofi Genzyme, Takeda, Teva Pharmaceuticals and WebMD. Royalties have been received for out-licensed monoclonal antibodies through the UTHSCH to Millipore (Chemicon International) Corporation since 1993.

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