# Infusion-Related Reactions With Ocrelizumab in the Phase III Studies


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## BACKGROUND

- The efficacy and safety of ocrelizumab (OCR) in Phase III studies in patients with relapsing multiple sclerosis (RMS) (OPERA I [NCT01247324] and OPERA II [NCT01412333])[1] and primary progressive multiple sclerosis (PPMS) (ORATORIO [NCT01194570])[2] have been reported previously
  - Infusion-related reactions (IRRs) were a very common adverse event (AE) in OCR recipients during controlled treatment in the OPERA I and OPERA II (n/N=283/825 [34.3%]); prespecified pooled analyses) and ORATORIO studies (n/N=194/486 [39.9%])
  - IRRs were more commonly reported during the first vs later infusions
- The purpose of these analyses was to define the pattern of OCR IRRs in the OPERA and ORATORIO studies

## METHODS

### *Studies*

- OPERA I and OPERA II (pooled analyses):[1] Patients with RMS were randomized 1:1 to receive double-blind, double-dummy treatment for 96 weeks with either OCR 600 mg intravenous (IV) every 24 weeks or interferon (IFN) β-1α 44 µg three times weekly (**Figure 1**)
  - The first OCR dose was administered as 2 × 300 mg infusions 14 days apart
- ORATORIO:[2] Patients with PPMS were randomized 2:1 to receive treatment for ≥120 weeks with either OCR 600 mg IV or matching placebo (PBO) every 24 weeks (**Figure 1**)
  - All OCR doses were administered as 2 × 300 mg infusions 14 days apart
- IRR management strategies within OPERA I, OPERA II and ORATORIO included: Pre-infusion prophylaxis (per-protocol; all patients, all infusions) with methylprednisolone (MP) 100 mg IV (or equivalent); additional analgesics/antipyretics and/or antihistamine were recommended
  - Permitted adjustments to infusion rate/treatment of symptoms

**For OPERA I/II and ORATORIO study design (Figure 1), scan here**

### *Statistics*

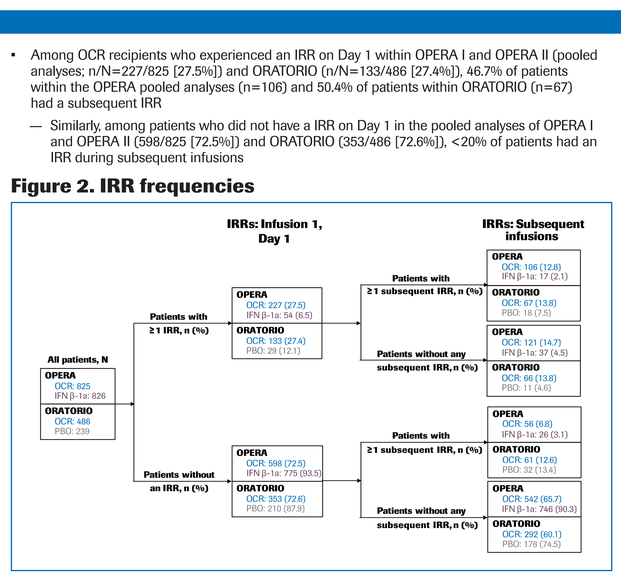
- Data from the identical OPERA studies were pooled as part of prespecified analyses; data from ORATORIO are reported directly
- Populations of special interest were:
  - Patients with at least one or multiple IRRs
  - Patients without an IRR on Day 1 who had at least one or multiple subsequent IRRs
  - Patients with at least one IRR on Day 1 with or without at least one subsequent IRR
- Subgroups of special interest were:
  - Premedication (MP alone, MP plus analgesic/antipyretics, MP plus antihistamines and analgesic/antipyretics)
  - Demographics (e.g. race, gender, baseline body weight)

## RESULTS

### *IRR Frequencies in OPERA I and OPERA II (Pooled Analyses) and ORATORIO*

- Overall, IRRs occurred more frequently in patients receiving OCR than in the respective comparator groups
  - OCR: OPERA, ≥1 IRR, n=283 (34.3%); >1 IRR, n=123 (14.9%); ORATORIO, ≥1 IRR, n=194 (39.9%); >1 IRR, n=95 (19.5%)
  - IFN β-1a: ≥1 IRR, n=80 (9.7%); >1 IRR, n=21 (2.5%)
  - PBO: ≥1 IRR, n=61 (25.5%); >1 IRR, n=28 (11.7%)
- Patients receiving OCR or IFN β-1a who had an IRR experienced the first event most frequently during the first infusion vs later infusions (**Figure 2**)
  - OCR: OPERA, 27.5% vs 6.8%; ORATORIO, 27.4% vs 12.6%
  - IFN β-1a: 6.5% vs 3.1%; PBO: 12.1% vs 13.4%
- Among OCR recipients who experienced an IRR on Day 1 within OPERA I and OPERA II (pooled analyses; n/N=227/825 [27.5%]) and ORATORIO (n/N=133/486 [27.4%]), 46.7% of patients within the OPERA pooled analyses (n=106) and 50.4% of patients within ORATORIO (n=67) had a subsequent IRR
  - Similarly, among patients who did not have a IRR on Day 1 in the pooled analyses of OPERA I and OPERA II (598/825 [72.5%]) and ORATORIO (353/486 [72.6%]), <20% of patients had an IRR during subsequent infusions

## Figure 2. IRR frequencies




IFN, interferon; IRR, infusion-related reaction; OCR, ocrelizumab; PBO, placebo.

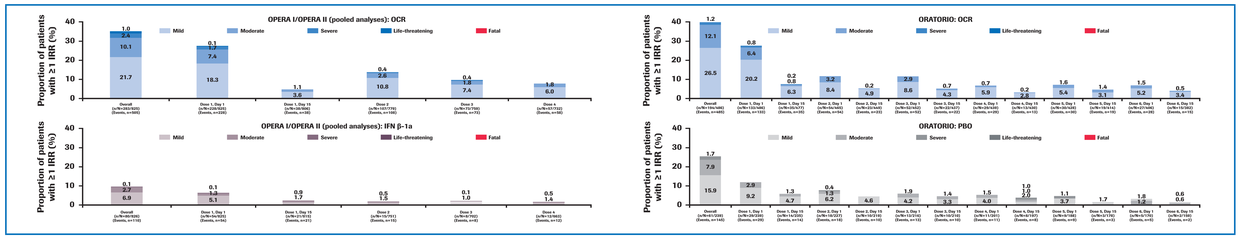
### *IRR Frequencies by Dose and Intensity in OPERA I and OPERA II (Pooled Analyses) and ORATORIO*

- The majority of IRRs in patients within the OCR treatment groups (OPERA pooled analyses and ORATORIO) and the respective comparator groups were mild to moderate and generally manageable (**Figure 3**)
  - OCR: A total of 20 IRRs (2.4%) within OPERA (pooled analyses) and 6 IRRs (1.2%) in ORATORIO were severe; of these, 14 (1.7%) and 4 (0.8%), respectively, occurred during the first infusion; there was one life-threatening IRR (OPERA) and no fatal IRRs
  - The life-threatening IRR (bronchospasm) occurred during the first infusion; the event resolved and the patient was withdrawn per protocol
- In OCR recipients, IRRs led to study withdrawal in 11 patients within OPERA (pooled analyses; all at the first infusion) and two patients in ORATORIO (one event at the first infusion)
  - IFN β-1a: One severe IRR (0.1%) occurred (first infusion); there were no life-threatening or fatal IRRs or IRRs leading to withdrawal
  - PBO: Four severe IRRs (1.7%) occurred, all of which were after the first infusion; there were no life-threatening or fatal IRRs
    - One patient withdrew due to an IRR after the third infusion
- In addition to frequency, the severity of IRRs in OCR recipients generally decreased with later infusions

### *IRR Frequencies by Dose and Pretreatment in OPERA I and OPERA II (Pooled Analyses) and ORATORIO*

- OCR-related IRR frequency patterns (vs comparators and occurrence at first vs later infusions) observed in the overall treatment arms of OPERA and ORATORIO remained when patients were stratified by pretreatment (**Table 1**)
- OCR recipients receiving pretreatment with MP plus antihistamines experienced fewer IRRs than patients receiving other pretreatments

## Figure 3. IRR frequencies by dose and intensity




IFN, interferon; IRR, infusion-related reaction; OCR, ocrelizumab; PBO, placebo.

## Table 1. IRR frequencies by dose and pretreatment

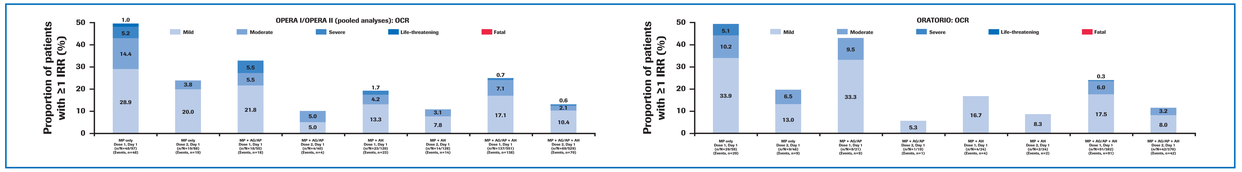
| IRR characteristic | Pretreatment regimen | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | MP alone | | MP + analgesic/antipyretic | | MP + antihistamine | | MP + analgesic/antipyretic + antihistamine | |
| **OPERA I/II (pooled analyses)** | **OCR (N=97)** | **IFN β-1a (N=88)** | **OCR (N=55)** | **IFN β-1a (N=49)** | **OCR (N=120)** | **IFN β-1a (N=127)** | **OCR (N=551)** | **IFN β-1a (N=561)** |
| **Total patients with an IRR, n (%)** | 51 (52.6) | 5 (5.7) | 24 (43.6) | 6 (12.2) | 35 (29.2) | 12 (9.4) | 172 (31.2) | 57 (10.2) |
| **Patients with an IRR on Day 1, n (%)** | 48 (49.5) | 4 (4.5) | 18 (32.7) | 4 (8.2) | 23 (19.2) | 5 (3.9) | 137 (24.9) | 41 (7.3) |
| With a subsequent IRR, n (%) | 20 (20.6) | 2 (2.3) | 9 (16.4) | 3 (6.1) | 9 (7.5) | 0 | 67 (12.2) | 12 (2.1) |
| Without a subsequent IRR, n (%) | 28 (28.9) | 2 (2.3) | 9 (16.4) | 1 (2.0) | 14 (11.7) | 5 (3.9) | 70 (12.7) | 29 (5.2) |
| **Patients without an IRR on Day 1, n (%)** | 49 (50.5) | 84 (95.5) | 37 (67.3) | 45 (91.8) | 97 (80.8) | 122 (96.1) | 414 (75.1) | 520 (92.7) |
| With a subsequent IRR, n (%) | 3 (3.1) | 1 (1.1) | 6 (10.9) | 2 (4.1) | 12 (10.0) | 7 (5.5) | 35 (6.4) | 16 (2.9) |
| Without a subsequent IRR, n (%) | 46 (47.4) | 83 (94.3) | 31 (56.4) | 43 (87.8) | 85 (70.8) | 115 (90.6) | 379 (68.8) | 504 (89.8) |
| **ORATORIO** | **OCR (N=59)** | **PBO (N=23)** | **OCR (N=21)** | **PBO (N=24)** | **OCR (N=24)** | **PBO (N=6)** | **OCR (N=382)** | **PBO (N=186)** |
| **Total patients with an IRR, n (%)** | 34 (57.6) | 4 (17.4) | 10 (47.6) | 9 (37.5) | 6 (25.0) | 0 | 144 (37.7) | 48 (25.8) |
| **Patients with an IRR on Day 1, n (%)** | 29 (49.2) | 3 (13.0) | 9 (42.9) | 4 (16.7) | 4 (16.7) | 0 | 91 (23.8) | 22 (11.8) |
| With a subsequent IRR, n (%) | 17 (28.8) | 2 (8.7) | 5 (23.8) | 4 (16.7) | 2 (8.3) | 0 | 42 (11.0) | 12 (6.5) |
| Without a subsequent IRR, n (%) | 12 (20.3) | 1 (4.3) | 4 (19.0) | 0 | 2 (8.3) | 0 | 49 (12.8) | 10 (5.4) |
| **Patients without an IRR on Day 1, n (%)** | 30 (50.8) | 20 (87.0) | 12 (57.1) | 20 (83.3) | 20 (83.3) | 6 (100) | 291 (76.2) | 164 (88.2) |
| With a subsequent IRR, n (%) | 8 (8.5) | 1 (4.3) | 1 (4.8) | 5 (20.8) | 2 (8.3) | 0 | 53 (13.9) | 26 (14.0) |
| Without a subsequent IRR, n (%) | 25 (42.4) | 19 (82.6) | 11 (52.4) | 15 (62.5) | 18 (75.0) | 6 (100) | 238 (62.3) | 138 (74.2) |

IFN, interferon; IRR, infusion-related reaction; MP, methylprednisolone; OCR, ocrelizumab; PBO, placebo.

### *OCR-Related IRR Frequency and Intensity by Pretreatment*

- Decreasing IRR severity, in addition to frequency, was also noted when OCR recipients experiencing an IRR were stratified by pretreatment (**Figure 4**)
  - The rate of severe IRRs in OCR recipients was lowest in patients receiving antihistamine-containing pretreatments
- No further subgroup effect (e.g. gender or age) were observed

## Figure 4. OCR-related IRR frequency and intensity by pretreatment




AG, analgesic; AH, antihistamine; AP, antipyretic; IRR, infusion-related reaction; MP, methylprednisolone; OCR, ocrelizumab.

## CONCLUSIONS

- **IRRs were a very common AE in patients receiving ocrelizumab in Phase III studies, and were:**
  - **Experienced by 34.3% and 39.9% of ocrelizumab recipients with RMS and PPMS, respectively**
  - **Infrequent in patients who did not have an IRR during the first ocrelizumab infusion**
  - **Generally mild to moderate in severity and manageable with pretreatment and symptomatic management**
  - **Least frequent in patients receiving pretreatment with MP (or equivalent) plus antihistamines vs other pretreatments**
- **Pretreatment with MP (or an equivalent corticosteroid) and an antihistamine is recommended to reduce the frequency and severity of IRRs; addition of an antipyretic may also be considered**

## DISCLOSURES

J de Seze has received consultancy fees and served as an expert for advisory boards for Alexion, Allergan, Almirall, Bayer, Biogen, Chugai, CSL Behring, F. Hoffmann-La Roche Ltd, Genzyme, LFB, Merck, Novartis, Sanofi and Teva. SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Bionure and Symbiotix and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations. L Kappos's institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for L Kappos's activities as principal investigator and member or chair of planning and steering committees or advisory boards for trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CLC Behring, F. Hoffmann-La Roche and Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharmaceutical, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; has received license fees for Neurostatus products and has received research grants from the European Union, Gianni Rubatto Foundation, Novartis Research Foundation, Roche Research Foundation, Swiss Multiple Sclerosis Society and Swiss National Research Foundation. X Montalban has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, been a steering committee member of clinical trials or served on advisory boards of clinical trials for Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos. C Pozzilli has served on scientific advisory boards for Actelion, Biogen, Genzyme, F. Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi and Teva, and has received consulting and/or speaking fees, research support and travel grants from Allergan, Almirall, Biogen, F. Hoffmann-La Roche Ltd, Genzyme, F. Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi and Teva. C Chognot is an employee of F. Hoffmann-La Roche Ltd. L Julian is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. H Zheng is an employee of Genentech, Inc. JS Wolinsky has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with AbbVie, Actelion, Alkermes, Biogen, Bionest, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma A/S, GeNeuro, MedDay Pharmaceuticals, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, Sanofi Genzyme; royalties are received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation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## REFERENCES


1. Hauser SL, *et al. N Engl J Med* 2017;376:221–234.
2. Montalban X, *et al. N Engl J Med* 2017;376:209–220.



The data on this poster have previously been presented at the 7th Joint European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Meeting; October 25–28, 2017; Paris, France.