EPO-403

Risk Factors for Serious Infections in Patients with MS Receiving Long-Term Ocrelizumab Treatment: Multivariate Analyses

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Introduction

Real-world studies have shown that people with multiple sclerosis (pwMS) have an increased risk of infections and infection-related hospitalisations compared with non-MS controls[1–6]

In patients treated with ocrelizumab (OCR), infections are among the most frequently reported adverse events, while serious infections (SIs) are infrequent and have generally been stable over time[7]

Understanding the characteristics and outcomes of SIs, and which factors drive the risk of SIs is fundamental for the correct management of OCR-treated patients, and can help guide treatment decisions

Aim

To understand the rates, clinical characteristics and outcomes of SIs in pwMS on continuous OCR, and to characterise the long-term risk factors associated with SIs in OCR-treated patients with relapsing MS (RMS) and primary progressive MS (PPMS)

Methods

Patient Populations and Clinical Cut-Off Dates

- **Descriptive analyses**: OCR all-exposure population, clinical cut-off date (CCOD) of 27 November 2020
- **Analyses of risk factors**: Phase III OPERA I/II (NCT01247324/NCT01412333) and ORATORIO (NCT01194570) populations; restricted to the period up to 3 January 2020, to allow characterisation unconfounded by the COVID-19 pandemic

- A Poisson Generalised Estimating Equation multivariate model with repeated measurements was constructed to examine risk factors for infections and SIs[a]
  - Factors included in the multivariate model were determined if p<0.2 in a univariate model
- Associations were reported using rate ratios and 95% confidence intervals (CIs)
- Separate models were built for patients with RMS and PPMS

[a]For full details of the univariate and multivariate models, please see the Supplemental Materials.

Results

Patient Disposition and Exposure

- As of November 2020, 5,688 patients (RMS=4,376; PMS=1,312) had received OCR, in 11 clinical trials
- 62.6% of patients were ongoing in the studies at the CCOD (n/N=3,563/5,688)
- Overall exposure was 21,674 patient years (PY), with 64.2% receiving at least 5 doses and 31.2% ≥10 doses
- Full patient disposition data can be found in the Supplemental Materials

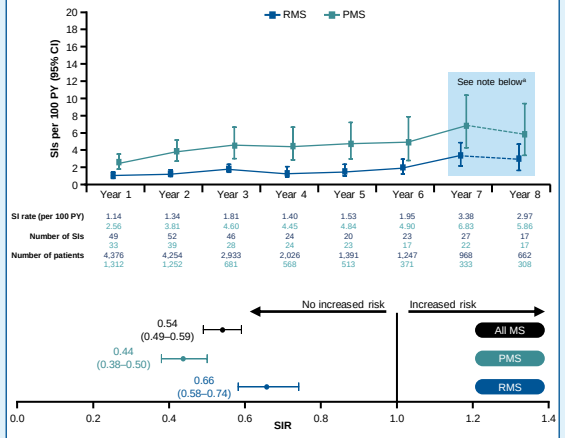
Patient Demographics and Clinical Characteristics at the Clinical Cut-Off Date

Characteristic	OPERA (N=1,448)[a]	ORATORIO (N=644)[a]	RMS all-exposure (N=4,376)[b]	PMS all-exposure (N=1,312)[b,c]
PY	7,862.2	3,562.0	16,635.1	5,039.5
Median time on treatment, years (range)	5.53 (0.0–8.2)	6.43 (0.1–8.7)	2.82 (0.0–11.7)	2.15 (0.0–9.7)
Age at baseline, mean (SD) years	38.1 (9.3)	45.8 (8.1)	35.86 (9.30)	47.13 (8.73)
Sex, n (%)				
Female	949 (65.5)	320 (49.7)	2,886 (66.0)	671 (51.1)
EDSS at OCR start,[d] mean (SD)	2.74 (1.37)	4.81 (1.28)	2.34 (1.30)[f]	4.89 (1.32)
<3.0, n (%)	810 (55.9)	12 (1.9)	2,849 (66.7)[f]	57 (4.3)
3.0–6.0, n (%)	625 (43.2)	529 (82.1)	1,368 (32.0)[f]	741 (56.5)
>6.0, n (%)	13 (0.9)	102 (15.8)[e]	57 (1.3)[f]	514 (39.2)
Number of comorbidities at last known follow-up, n (%)				
None	534 (36.9)	202 (31.4)	2,680 (61.2)	765 (58.3)
1	462 (31.9)	171 (26.6)	1,146 (26.2)	313 (23.9)
≥2	452 (31.2)	271 (42.1)	550 (12.6)	234 (17.8)

For additional patient demographic and clinical characteristics data, please see the Supplemental Materials.
[a]CCOD: 3 January 2020; [b]CCOD: 27 November 2020; [c]Includes patients with PPMS (n=979) and secondary progressive MS (n=333); [d]Last valid assessment prior to OCR treatment in the double-blind period and in the open-label extension for patients originally randomised to the OCR arm and switchers, respectively; [e]n=1 (0.2%) had a missing EDSS score in ORATORIO; [f]n=4,274.
CCOD, clinical cut-off date; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SD, standard deviation.

Results

SI Rates Fluctuated Over Time



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
SI rate (per 100 PY)	1.14	1.34	1.81	1.40	1.53	1.95	3.38	2.97
	2.56	3.81	4.60	4.45	4.84	4.90	6.83	5.86
Number of SIs	49	52	46	24	20	23	27	17
	33	39	28	24	23	17	22	17
Number of patients	4,376	4,254	2,933	2,026	1,391	1,247	968	662
	1,312	1,252	681	568	513	371	333	308

- Calculated standardised incidence ratios indicated no excess in the incidence of SIs in the OCR-treated RMS or PMS populations[b] compared with the AOK cohort,[c] a well-characterised, contemporaneous, real-world cohort of 4,250 pwMS in Germany[d]

[a]Patients with exposure above 8 years are not represented; across Years 9–12 of exposure, 27 SIs were reported. The increase during Year 7 in patients with RMS is driven by n=8 COVID cases (when COVID cases are excluded, the rate is 2.38 SIs per 100 PY instead of 3.38 SIs per 100 PY), and by a greater number of cases of urinary tract infections and urosepsis in patients with PMS. Exposure in PY during Year 8 is limited for meaningful interpretation; therefore, these data are presented with dotted lines; [b]OCR all-exposure populations; [c]The AOK cohort was used for real-world comparisons, patient characteristics: Female, 72.3%; mean (SD) age, 51.8 (15.2); no. of comorbidities, 0, 30.1%; 1, 26.7%; ≥2, 43.2%; please see Supplemental Materials for further information. Clinical cut-off date: 27 November 2020.
CI, confidence interval; MS, multiple sclerosis; OCR, ocrelizumab; PMS, progressive multiple sclerosis; PY, patient years; RMS, relapsing multiple sclerosis; SD, standard deviation; SI, serious infection; SIR, standardised incidence ratio.

SIs in the RMS and PMS All-Exposure Population[a]

TYPE OF MS: The overall rates of SIs per 100 PY were significantly higher in PMS vs RMS: 4.25 (95% CI: 3.70, 4.86) vs 1.65 (95% CI: 1.46, 1.85)

IDENTIFIED PATHOGENS: The majority of SIs were of bacterial origin (63.9%, n=312/488), followed by viral (21.5%, n=105/488)

SEVERITY: The majority of SIs were severe (RMS, 65.7%; PMS, 65.9%), while approximately 20% were mild or moderate

RESOLUTION: Almost all SIs were reported as resolved (RMS: 87.2%, n=239/274; PMS: 90.2%, n=193/214), with resolution observed for 25.5% (n=117/458) and 53.1% (n=243/458) of all SIs within 7 and 14 days, respectively

RMS

The most common SIs per 100 PY (95% CI):

Lower respiratory tract infections	0.28 (0.21, 0.38)
Urinary tract infections	0.27 (0.20, 0.36)
Abdominal/ gastrointestinal infections	0.25 (0.18, 0.34)

PMS

The most common SIs per 100 PY (95% CI):

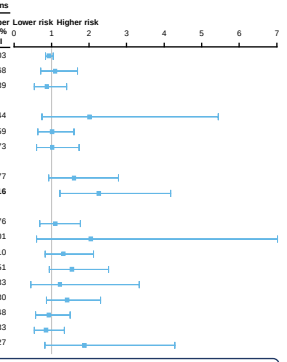
Urinary tract infections	1.17 (0.89, 1.51)
Lower respiratory tract infections	0.60 (0.40, 0.85)
Sepsis	0.56 (0.37, 0.80)

[a]For more information please see Supplemental Materials.

Multivariate Model for Risk of SIs in OPERA (RMS)

Serious infections

Covariate	RR	Lower 95% CI	Upper 95% CI
Time on OCR (per year)	0.92	0.82	1.03
Male (vs female)	1.08	0.70	1.68
≥45 years old at OCR start (vs <45)	0.86	0.53	1.39
BMI (vs 18.5–25.0 kg/m²)			
<18.5 (underweight)	2.01	0.74	5.44
>25.0 (overweight/obese)	0.99	0.62	1.59
USA (vs ROW)	1.01	0.59	1.73
Number of comorbidities (vs 0)			
1	1.59	0.91	2.77
≥2	**2.24**	**1.21**	**4.16**
EDSS (vs <3.0)			
3.0–6.0	1.09	0.68	1.76
>6.0	2.03	0.59	7.01
>10 years disease duration (vs ≤10)	1.31	0.81	2.10
Relapse in year prior to OCR start (vs no relapse)	1.53	0.93	2.51
Relapse during treatment (vs no relapse)	1.21	0.44	3.33
Prior DMT treatment (vs none)	1.40	0.86	2.30
IFN ß-1a arm (vs OCR arm)	0.91	0.56	1.48
IgM<LLN 0.4 g/l (vs ≥LLN)	0.84	0.53	1.33
IgG<LLN 5.65 g/l (vs ≥LLN)	1.86	0.81	4.27



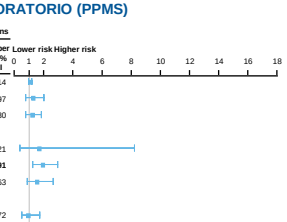
- Time on OCR was not associated with a higher risk of SIs; only the presence of ≥2 comorbidities was associated with an increased risk of SIs

Clinical cut-off date: 3 January 2020.
BMI, body mass index; CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; Ig, immunoglobulin; LLN, lower limit of normal; OCR, ocrelizumab; RMS, relapsing multiple sclerosis; ROW, rest of world; RR, rate ratio; SI, serious infection.

Multivariate Model for Risk of SIs in ORATORIO (PPMS)

Serious infections

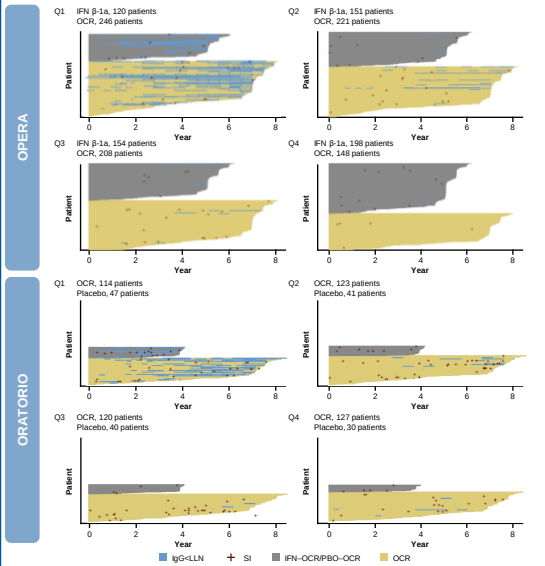
Covariate	RR	Lower 95% CI	Upper 95% CI
Time on OCR (per year)	1.03	0.92	1.14
Male (vs female)	1.22	0.76	1.97
≥50 years old at OCR start (vs <50)	1.16	0.75	1.80
BMI (vs 18.5–25.0 kg/m²)			
<18.5 (underweight)	1.65	0.33	8.21
>25.0 (overweight/obese)	**1.90**	**1.24**	**2.91**
USA (vs ROW)	1.50	0.86	2.63
Number of comorbidities (vs 0)			
1	0.90	0.48	1.72
≥2	1.37	0.81	2.33
EDSS (vs <3.0)			
3.0–6.0	1.83	0.70	4.76
>6.0	**6.08**	**2.62**	**16.33**
>6 years disease duration (vs ≤6)	1.11	0.63	1.94
Prior DMT treatment (vs none)	0.93	0.50	1.75
Placebo arm (vs OCR arm)	1.82	0.94	3.52
IgM<LLN 0.4 g/l (vs ≥LLN)	**1.64**	**1.05**	**2.55**
IgG<LLN 5.65 g/l (vs ≥LLN)	1.30	0.62	2.69



- Time on OCR was not associated with a higher risk of SIs; covariates that were associated with an increased risk of SIs in patients with PPMS were being overweight or obese, having an EDSS >6.0 and having abnormal IgM levels
  - Abnormal IgM levels may be a chance finding due to skewness of data, given that 5% of patients with IgM<LLN accounted for 40% of associated SIs
- A trend towards an increased risk (p=0.07) was observed for patients who switched from placebo

Clinical cut-off date: 3 January 2020. BMI, body mass index; CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Ig, immunoglobulin; LLN, lower limit of normal; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; ROW, rest of world; RR, rate ratio; SI, serious infection.

Periods of IgG<LLN and SI Events Occurring in Baseline IgG Quartiles During OCR Treatment[a]



- Periods of IgG<LLN were mostly transient (blue horizontal lines). Rates of SIs were similar across different quartiles both for patients with RMS and PPMS (red crosses; for actual rates see Supplementary Materials)
- Over a period of up to 7.5 years of treatment with OCR, reduction in absolute IgG levels was greater in patients with higher baseline levels, but a similar relative reduction was observed across all quartiles; the temporal evolution of IgG across the different quartiles followed a pattern that could be better explained by an exponential decay model, suggesting that the decrease in IgG levels plateaus in patients receiving long-term treatment with OCR (see Supplementary Materials)

[a]**Continuous OCR and switchers.** Each horizontal yellow line represents OCR exposure of individual patients who were initially randomised to OCR. Each grey line represents OCR exposure of individual patients who were initially randomised to either IFN (OPERA) or placebo (ORATORIO) and then switched to OCR. LLN=5.65 g/l. The majority of SIs do not occur during periods of IgG<LLN.
IFN, interferon; IgG, immunoglobulin G; LLN, lower limit of normal; OCR, ocrelizumab; PBO, placebo; Q, quartile; SI, serious infection.

Conclusions

- Over a period of **up to 12 years of ocrelizumab** treatment, **SI rates remained stable and infrequent**, with only minor fluctuations observed over time
- After adjusting other risk factors, **time on ocrelizumab was not associated with an increased risk of SIs** in patients with either RMS or PPMS
- Risk factors for SIs varied between RMS and PPMS cohorts
  - **Having ≥2 comorbidities** was associated with an increased risk in RMS and PPMS
  - **Body mass index (BMI), EDSS and IgM<LLN** were associated with an increased risk in PPMS; however, 5% of patients with IgM<LLN accounted for 40% of associated SIs
  - Addressing potentially modifiable risk factors, such as comorbidities and BMI, may reduce the risk of SIs in patients with RMS and PPMS
- **SIs** were largely **manageable** with **favourable outcomes**

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CONFLICTS OF INTEREST

T Derfuss has served on scientific advisory boards, steering committees and data safety monitoring boards for Actelion, Alexion, Biogen, Celgene, Genzyme, GeNeuro, Merck, Mitsubishi Pharma, Novartis, Roche, Octapharma and MedDay; has received travel and/or speaker honoraria from Biogen, Genzyme, Merck, Novartis, Roche and Merck-Serono; has received research support from Alexion, Biogen, Novartis, Roche, the Swiss MS Society and the Swiss National Foundation. **R Bermel** has served as a consultant for Biogen, EMD Serono, Genzyme, Genentech, Novartis and Viela Bio. He receives research support from Biogen, Genentech and Novartis; and shares rights to intellectual property underlying the Multiple Sclerosis Performance Test, currently licensed to Qr8 Health and Biogen. **C-J Lin** is an employee of F. Hoffmann-La Roche Ltd. **SL Hauser** serves on the Board of Directors for Neurona and on Scientific Advisory Boards for Accure, Alector and Annexon, and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd and Novartis for CD20-related meetings and presentations. **L Kappos**' institution (University Hospital Basel) has received the following exclusively for research support: Steering committee, advisory board and consultancy fees (Actelion, Bayer HealthCare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Sanfilrera, Shionogi and TG Therapeutics); speaker fees (Bayer HealthCare, Biogen, Merck, Novartis, Roche and Sanofi); support of educational activities (Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire and Teva); license fees for Neurostatus products; and grants (Bayer HealthCare, Biogen, European Union, InnoSwiss, Merck, Novartis, Roche, Swiss MS Society and Swiss National Research Foundation). **T Vollmer** has received compensation for consultancy from Biogen, Genentech/Roche, and Novartis and has received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen, Anokion, Genentech, F. Hoffmann-La Roche Ltd, GW Pharma and TG Therapeutics, Inc. **G Comi** has received consulting and speaking fees from Novartis, Sanofi-Genzyme, Genzyme Corporation, Merck KGaA, Merck-Serono SpA, Celgene Group, F. Hoffmann-La Roche Ltd, Almirall SpA and Janssen. **G Giovannoni** has received personal compensation for serving as a consultant for F. Hoffmann-La Roche Ltd, AbbVie, Actelion, Atara Biotherapeutics, Biogen, Celgene, Sanofi-Genzyme, Genentech, Inc., GlaxoSmithKline, Merck-Serono, Novartis and Teva; has received personal compensation from Elsevier for serving as an editor on MSARDs; and has received financial support for research activities from F. Hoffmann-La Roche Ltd, Biogen, Merck, Merck-Serono, Novartis, Sanofi-Genzyme and Takeda. **H-P Hartung** has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, F. Hoffmann-La Roche Ltd, GeNeuro SA, Genzyme, MedImmune, Merck-Serono, Novartis, Octapharma, Sanofi-Genzyme, Teva, TG Therapeutics and Viela Bio. **J Wang** is an employee of F. Hoffmann-La Roche Ltd. **N Jessop** is an employee of F. Hoffmann-La Roche Ltd. **C Chognot** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **L Craveiro** is an employee of and shareholder in F. Hoffmann-La Roche Ltd. **A Bar-Or** has received consulting fees from Actelion, Atara Biotherapeutics, Biogen Idec., Celgene/Receptos, Genentech/Roche, MAPI, Medimmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme, GlaxoSmithKline and Brainstorm, has carried out contracted research for Genentech and Biogen; and receives a salary from The University of Pennsylvania, Perelman School of Medicine. This study was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance for this presentation was provided by Articulate Science, UK, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

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Scan the QR code to download a PDF of this poster and to access the Supplemental Material.