Ocrelizumab and infections

Overview

- PwMS are at greater risk of developing, and being hospitalised for, infections than the general population[1–3]

- In clinical trials, infections were a frequently reported AE[4,5]
- However, no increased risk of serious infections with OCR vs IFN β-1a or placebo was observed[4,5]
- Incidence rates were higher in the PPMS than RMS population[6]

- The incidence and type of infections seen in the post-marketing setting (data cut-off: March 2020) is in line with the clinical trial data (data cut-off: November 2020)[7]

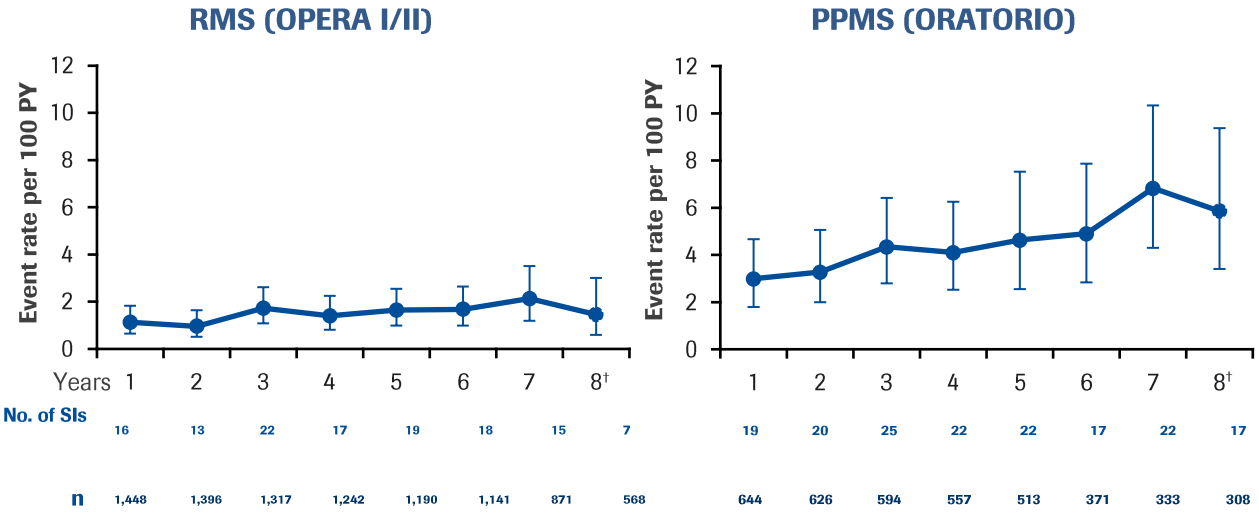
Clinical trials (controlled treatment period and open-label extension)

Incidence rates of SI in ocrelizumab clinical trials per 100 PY[6]

Adverse event Rate per 100 PY (95% CI)	CTP*				CTP/OLE†		OCR all-exposure population‡
	OPERA		ORATORIO		OPERA	ORATORIO	
	IFN β-1a	OCR	Placebo	OCR	OCR	OCR	
Total no. of patients/PY	826/1,399	825/1,448	239/729	486/1,606	1,448/8,806	644/3,937	5,688/ 21,675
Infections and infestations	**67.8** (63.5–72.2)	**84.5** (79.9–89.4)	**72.5** (66.5–79.0)	**70.8** (66.8–75.0)	**70.0** (68.3–71.8)	**72.7** (70.1–75.4)	**71.8** (70.7–73.0)
Serious infections§	**1.79** (1.16–2.64)	**0.83** (0.43–1.45)	**3.02** (1.89–4.57)	**2.74** (1.99–3.68)	**1.45** (1.21–1.73)	**4.34** (3.72–5.05)	**2.00** (1.82–2.20)

- In the OCR all-exposure population the rate of SIs was consistent with rates of infection-related hospitalisations reported in a real-world MS cohort[4–6]
- No new or particular patterns of SIs were identified by year in either the RMS or PPMS OCR-treated patients[4–6]
- The most frequently reported SIs overall were consistent with the frequently reported SIs reported for each year[4–6]
- In PPMS, the rate of SIs remained higher than RMS; over time, the underlying disease condition (e.g. increasing disability, age, comorbidities) appears to drive this possible increase[4–6]
  - The majority of SIs were typical in character, resolved, and were not treatment limiting

Phase III DBP/OLE: Incidence rates per 100 PY of SI over time in ocrelizumab clinical trials over 8 years*,[6]



Total serious infections: n=434
SI rate per 100 PY: 2.00 (1.82–2.20)

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Post-marketing experience[†,7]

As of March 2020…

~158,092 patients with RMS and PPMS have started OCR outside of RCTs

Corresponding to an exposure of **~190,651 PY**

A **total of 3,721 serious events** of infections and infestations were reported in patients receiving OCR

- **No new findings** related to the type or pattern of SIs were identified
- In these post-marketing case reports, the most commonly reported SIs by preferred terms were **UTI and pneumonia**, which **is in line with clinical trial data**

Footnotes

Table 1
AEs were classified according to MedDRA versions 18.0, 18.1 and 22.1. Multiple occurrences of the same AE in one patient are counted multiple times, except for malignancies.

*Data as of April–July 2015;
[†]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the phase III studies, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2020);
[‡]Includes patients who received any dose of OCR during the CTP and associated OLE periods of the phase II and phase III studies plus VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, LIBERTO and CONSONANCE, including patients originally randomised to comparator (IFN β-1a or placebo) who switched to open-label OCR treatment (data as of November 2020;
[§]Serious infections are defined using AEs falling into the MedDRA SOC 'Infections and infestations', and using 'Is the event nonserious or serious?' from the AE case report form.

Figure 1
Exposure to ocrelizumab in the phase 3 pooled RMS and PPMS populations in total PY. Investigator text for AEs was encoded using MedDRA versions 18.0, 18.1, and 22.1. Multiple occurrences of the same AE in one patient are counted multiple times. SIs are defined as serious AEs reported using terms in the MedDRA SOC Infections and infestations. 95% CIs were calculated using an exact method based on the Poisson distribution. Patients are considered in the ongoing year, e.g. Year 7 contains patients completing at least 6 years in the study and ongoing during the seventh year.

*Yearly rates of serious infections in patients with RMS or PPMS treated with ocrelizumab during the CTPs and associated OLE periods of the phase III trials (OPERA 1, OPERA 2, and ORATORIO) for a period of up to 7 years. It includes patients randomised to ocrelizumab and patients who received PBO or IFN β-1a during the CTPs, but subsequently switched to OCR at the beginning of the OLE periods (N=2,092; 10,924 PY);
[†]The exposure in PY during Year 8 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

Post-marketing
[†]There are well-recognised limitations that should be considered when interpreting spontaneous post-marketing safety reports, including events that may not be causally related to drug exposure; in the real-world setting, events are frequently confounded by factors such as multiple drug use and the presence of pre-existing comorbidities; reporting bias may exist for more significant outcomes, which may result in an overrepresentation of the more serious outcomes; and reporting rates can be stimulated by external factors, such as press reports.

The causes of infections are recorded as reported to the company; while the company follows up on all reports to identify the cause, an exact diagnosis is not always possible. Some of the investigations remain ongoing and, therefore, the information may be subject to change.

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Footnotes (cont.)

Abbreviations

AE, adverse event; CTP, controlled treatment period; DBP, double-blind period; IFN β-1a, interferon beta-1a; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient-years; pwMS, people with MS; RCT, randomised controlled trial; RMS, relapsing MS; SI, serious infection; SOC, standard of care; UTI, urinary tract infection.

References

1. Wijnands JMA, *et al. Mult Scler* 2017;23:1506–16;
2. Nelson RE, *et al. Int J MS Care* 2015;17:221–30;
3. Wijnands JMA, *et al. J Neurol Neurosurg Psychiatry* 2018;89:1050–6;
4. Hauser SL, *et al. N Engl J Med* 2017:376:221–34;
5. Montalban X, *et al. N Engl J Med* 2017;376:209–20;
6. Hauser SL, *et al.* Presented at ECTRIMS 2021 (Poster P724);
7. Roche data on file.

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