Ocrelizumab and Infections

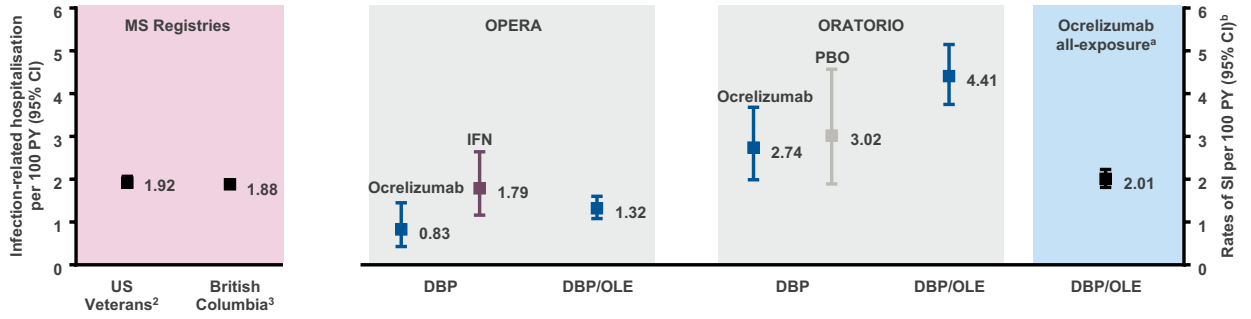
Background Infection Rates in the MS Population[1-3]

- Patients with MS have a higher risk of infection and hospital admission rates for infection compared with the general population
- A study assessing data from The Department of Veterans Affairs included 7743 veterans with MS and 30,972 without MS. Incidence rates (95% CI) for SI were 1.92 (1.76, 2.08) per 100 PY for those with MS vs 1.03 (0.98, 1.09) per 100 PY for those without MS
- A population-based study assessing data from British Columbia found that exposure to any DMT (7682.1 PY) compared with no exposure (51,662.8 PY) was not associated with a significantly altered hazard for an infection-related hospitalisation (adjusted HR, 0.98; 95% CI, 0.77, 1.26)

Clinical Trials (Controlled Treatment Period and Open-Label Extension)

- In the controlled treatment period of the ocrelizumab phase 3 clinical trials, infections were one of the most frequently reported AEs[4,5]
  - In the phase 3 trials, no increased risk of SI with ocrelizumab vs IFN β-1a or placebo was observed
- The rate (95% CI) of SI was **2.01 (1.81, 2.23)** per 100 PY in the ocrelizumab all-exposure population[6]*
  - The most common SIs were UTI, pneumonia, and cellulitis[6,7]
  - The majority of SIs were of grade ≤3 intensity and resolved without sequelae; most (57.7%) resolved ≤2 weeks and were not treatment limiting[6]
  - The majority of SIs (96.2%) resolved without treatment discontinuation

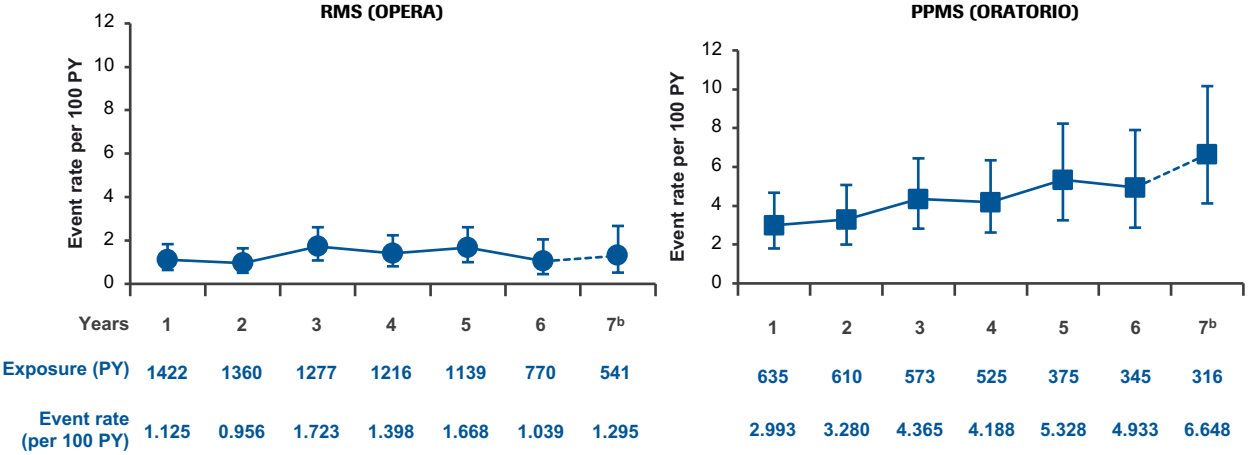
Figure 1: Incidence Rates of SI in Ocrelizumab Clinical Trials vs Infection-Related Hospitalisation from Select Registries per 100 PY



[a]Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the phase 2 and phase 3 studies plus VELOCE, CHORDS, CASTING, LIBERTO, OBOE, CONSONANCE, and ENSEMBLE (data as of January 2020).
[b]Includes SI without hospitalisation.

- No new or particular patterns of SI were identified by year in patients either with RMS or PPMS and treated with ocrelizumab[6] (Figure 2)
  - In the PPMS population, the rate of SI per 100 PY by year remained higher than in the RMS population
  - The frequently reported SIs overall were consistent with the frequently reported SIs reported each year

Figure 2: Phase 3 DBP/OLE: Incidence Rates per 100 PY of SI Over Time in Ocrelizumab Clinical Trials[a]



Years	1	2	3	4	5	6	7[b]
Exposure (PY)	1422	1360	1277	1216	1139	770	541
Event rate (per 100 PY)	1.125	0.956	1.723	1.398	1.668	1.039	1.295

Years	1	2	3	4	5	6	7[b]
Exposure (PY)	635	610	573	525	375	345	316
Event rate (per 100 PY)	2.993	3.280	4.365	4.188	5.328	4.933	6.648

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, eg, Year 7 contains patients completing at least 6 years in the study and ongoing during the seventh year.
[a]Yearly rates of serious infections in patients with RMS or PPMS treated with ocrelizumab during the CTPs and associated OLE periods of the phase 3 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).
[b]The exposure in PY during Year 7 is limited for meaningful interpretation, so these data are presented in the plots with dotted lines.

Serum Immunoglobulin Levels[7]

- As of January 2020, at approximately 7 study years of ocrelizumab exposure in the phase 3 DBP and OLE group, a reduction in serum Ig levels was observed at an approximate mean rate of 3–4% per year for IgG; however, for the majority of patients, Ig levels remained above LLN (Table 1)
- An apparent association between decreased levels of IgG (and less so for IgM or IgA) and SI was observed, but overall incidence and numbers of SIs were low
- The type and outcome of SIs observed during episodes of Ig <LLN were consistent with the overall SIs observed in patients without decreased IgG[7]
  - Of 2092 patients treated with ocrelizumab in the phase 3 DBP and OLE, 198 patients (9.5%) experienced IgG <LLN, and 15 patients (0.7%) experienced a total of 20 SIs with IgG <LLN
  - No pattern was identified (type of SI, latency to ocrelizumab start, duration of SI)
  - All SIs recovered (no fatal outcome)

Table 1: Rates of SI per 100 PY by IgM, IgG, and IgA levels[a]

	IgM		IgG		IgA	
	<LLN	≥LLN	<LLN	≥LLN	<LLN	≥LLN
Patients (n)	813	1279	198	1894	154	1938
Episodes (n)	1092	2460	356	2305	208	2153
PY	2573	8954	352	11,174	351	11,164
No. of SIs	88	173	20	241	9	252
Rates of SI per 100 PY	3.42	1.93	5.68	2.16	2.57	2.26

January 2020 data cut. SIs are defined as serious AEs reported using terms in the MedDRA SOC Infections and infestations. [a]Includes patients who received any dose of ocrelizumab during the controlled treatment and associated OLE periods of the phase 3 OPERA and ORATORIO studies. Multiple occurrences of the same AE in one individual are counted multiple times. Exposure of <LLN is counted from the day lab <LLN until the day lab ≥LLN; exposure gap is excluded from PY.

- Information on confirmed cases of reported PML in ocrelizumab-treated patients can be found on the PML page of the website

Post-Marketing Experience[7†]

- As of 27 March 2020, ~158,092 patients with RMS and PPMS had started ocrelizumab globally outside of clinical trials (ie, post-marketing only), corresponding to an exposure of ~190,651 PY
  - A total of 3721 serious events of infections and infestations were reported in patients receiving ocrelizumab globally outside of clinical trials
  - 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

Prescribing Information

Indications vary in different countries. The local prescribing information from your country is the primary source of information on the known and potential risks associated with ocrelizumab.

Footnotes: *Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the phase 2 and phase 3 studies plus VELOCE, CHORDS, CASTING, LIBERTO, OBOE, CONSONANCE, and ENSEMBLE (data as of January 2020).

†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.

Abbreviations: AE=adverse event; CI=confidence interval; CTP=controlled treatment period; DBP=double-blind period; DMT=disease-modifying treatment; HR=hazard ratio; IFN=interferon; Ig=immunoglobulin; LLN=lower limit of normal; MedDRA=Medical Dictionary for Regulatory Activities; MS=multiple sclerosis; OCR=ocrelizumab; OLE=open-label extension; PBO=placebo; PML=progressive multifocal leukoencephalopathy; PPMS=primary progressive multiple sclerosis; PY=patient-years; RMS=relapsing multiple sclerosis; SI=serious infection; SOC=system organ class; UTI=urinary tract infection.

References: 1. Wijnands JMA, et al. *Mult Scler.* 2017;23:1506-1516; 2. Nelson RE, et al. *Int J MS Care.* 2015;17:221-230; 3. Wijnands JMA, et al. *J Neurol Neurosurg Psychiatry.* 2018;89: 1050-1056; 4. Hauser SL, et al. *N Engl J Med.* 2017:376:221-234; 5. Montalban X, et al. *N Engl J Med.* 2017;376:209-220; 6. Hauser SL, et al. Presented at MSVirtual2020 (8th Joint ACTRIMS-ECTRIMS Congress) (P0389); 7. Roche data on file.

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