Effect of Ocrelizumab on Vaccine Responses in Patients With Multiple Sclerosis

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BACKGROUND

- Ocrelizumab (OCR) is a high-efficacy treatment approved for relapsing multiple sclerosis (RMS)[1] and is the first approved treatment for primary progressive multiple sclerosis
- OCR selectively depletes CD20+ B cells while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity[2–5]
- In the Phase III OPERA I and OPERA II studies in patients with RMS, pre-existing antibody titres against common viral and bacterial antigens were similar in OCR and high-dose interferon (IFN) β-1a recipients at baseline, and were maintained throughout the 96-week double-blind treatment period[6]
- There is a need to further understand the impact of OCR on the response to vaccines

OBJECTIVE

- VELOCE (NCT02545868) is a Phase IIIb study being conducted in the USA and Canada to evaluate the effects of OCR on humoral responses to selected vaccines (**Table 1**) in patients with RMS

Table 1. Vaccines and neoantigen used in VELOCE

VELOCE vaccines/neoantigen[a]	Response pathway
Tetanus toxoid–containing vaccine	Mainly T-cell–dependent response to a known antigen
23-valent pneumococcal polysaccharide vaccine	Mainly B-cell–dependent response
13-valent pneumococcal conjugate vaccine	Response to a booster of 23-PPV
Seasonal influenza (inactivated)[b]	Response to a clinically relevant vaccine
Keyhole limpet haemocyanin	Humoral response to a neoantigen

[a]Commercially available vaccines were used; all vaccines were administered in the deltoid muscle as a single intramuscular injection (KLH was administered subcutaneously); [b]Locally available tri- or quadrivalent World Health Organization-recommended seasonal influenza vaccines (2015/2016 or 2016/2017) for the Northern Hemisphere were used.
KLH, keyhole limpet haemocyanin; PPV, 23-valent pneumococcal polysaccharide vaccine.

METHODS

Study Endpoints

- Primary endpoint: proportion of patients with a positive response (immunoglobulin G [IgG]) to tetanus toxoid (TT)-containing vaccine 8 weeks after TT booster vaccine administration
  - Assessed at 4 weeks post-vaccination as a secondary endpoint
- Secondary endpoints included:
  - **23-valent pneumococcal polysaccharide vaccine (23-PPV) and 13-valent pneumoccal conjugate vaccine (13-PCV)**: proportion of patients with a positive response against an individual pneumococcal serotype 4 weeks after vaccination
  - **Influenza vaccine**: proportion of patients treated with OCR who achieve seroprotection at 4 weeks post-vaccination compared with patients in the Control group
  - **Keyhole limpet haemocyanin (KLH)**: mean levels of anti-KLH antibody (IgG and IgM) in all patients during the immunisation study period (ISP; immediately prior and 4, 8 and 12 weeks after the last administration of KLH)

Study Design

- VELOCE has five study periods, which include: screening, immunisation, optional OCR extension, safety follow-up and continued B-cell monitoring (**Figure 1**)
- Patients were randomised (2:1) to receive one dose of OCR 600 mg (per prescribing information), or remain on IFN β or no disease-modifying therapy (DMT; Control group) during the ISP
  - Patients in the OCR group were assigned to OCR 1 or OCR 2 at randomisation
- Vaccinations in the OCR group were started at Week 12 when patients were B-cell depleted; vaccinations in the Control group were started on Day 1

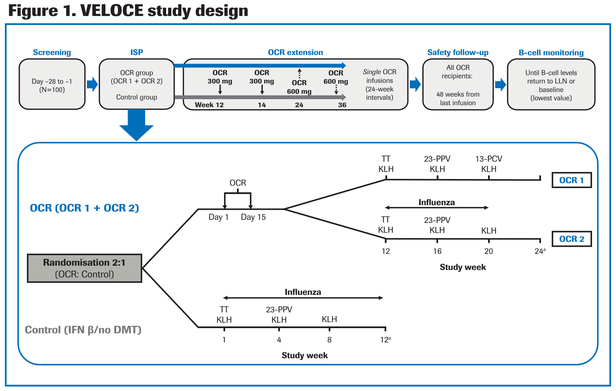
Inclusion/Exclusion Criteria

- Patients were aged 18–55 years, had a diagnosis of RMS (McDonald Criteria, 2010) and a baseline Expanded Disability Status Scale score at screening of 0–5.5
- Patients had received ≥1 vaccination with a TT-containing vaccine >2 years prior to screening
- Patients were excluded if they had received any pneumococcal vaccine <5 years prior to screening or a live vaccine <6 weeks prior to randomisation, or had previous exposure to KLH

Analysis Population

- We report findings from the Observed Cases population (all patients completing the ISP) during the ISP (first patient, first visit: 27 October 2015; last patient, last visit: 14 February 2017 [effective clinical cut-off date])
- There was no formal assessment of non-inferiority; comparisons and 95% CIs were calculated via the normal approximation method

Figure 1. VELOCE study design



[1]ISP duration: OCR group (OCR 1+ OCR 2), 24 weeks; Control group, 12 weeks.
13-PCV, 13-valent pneumococcal conjugate vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; DMT, disease-modifying therapy; IFN, interferon; ISP, immunisation study period; KLH, keyhole limpet haemocyanin; LLN, lower limit of normal; OCR, ocrelizumab; TT, tetanus toxoid-containing vaccine.

RESULTS

Baseline Demographic and Disease Characteristics

- Baseline demographic and disease characteristics were generally well balanced (**Table 2**)
  - There was a lower proportion of female patients in the OCR group than in the Control group
  - The mean number of T1 gadolinium-enhancing lesions at baseline was higher in patients in the OCR group than in the Control group
- Twelve patients (35%) randomised to the Control group remained on IFN β during the ISP

Table 2. Baseline demographic and disease characteristics

Parameter	OCR 600 mg (all) N=68	Control (IFN β/no DMT) N=34
Age, years, mean (SD)	39.7 (8.9)	41.4 (7.9)
Female, n (%)	45 (66.2)	27 (79.4)
Caucasian, n (%)	64 (94.1)	30 (88.2)
BMI, kg/m², mean (SD)	28.9 (6.7)[a]	26.6 (5.7)[b]
Duration since MS symptom onset, years, mean (SD)	8.9 (7.1)	9.5 (5.9)
Duration since RMS diagnosis, years, mean (SD)	6.6 (6.6)	7.1 (5.2)
Baseline EDSS score, mean (SD)	2.7 (1.3)	2.3 (1.4)
Number of T1 gadolinium-enhancing lesions, mean (SD)	2.9 (10.9)[c]	0.6 (2.7)
Number of T2 lesions, mean (SD)	57.9 (45.4)[d]	45.5 (28.6)
T2 lesion volume, cm³, mean (SD)	10.8 (13.3)[d]	7.5 (8.2)

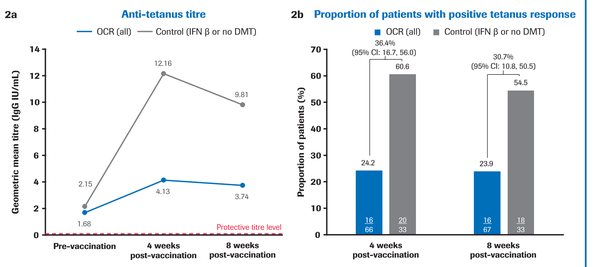
[a]n=64; [b]n=33; [c]n=65; [d]n=66.
BMI, body mass index; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; RMS, relapsing multiple sclerosis.

- Vaccination/passive immunisation histories in the OCR and Control groups were comparable
- All patients completed the ISP and entered the optional OCR extension period; all patients randomised to OCR received a single dose (600 mg)

Response (IgG) to Tetanus Toxoid-Containing Vaccine

- Pre-vaccination geometric mean anti-tetanus (IgG) antibody levels were comparable between treatment groups (**Figure 2a**)
- Geometric mean IgG levels 4 and 8 weeks post-vaccination were lower in patients receiving OCR, compared with those in the Control group (**Figure 2a**)
- The proportion of patients with a positive response at 4 and 8 weeks was lower in those who received OCR versus Control (**Figure 2b**)
- All patients with a known response were seroprotected (IgG ≥0.1 IU/mL) 4 and 8 weeks after vaccination, including three patients not seroprotected prior to vaccination (all OCR)

Figure 2. Response (IgG) to tetanus toxoid–containing vaccine

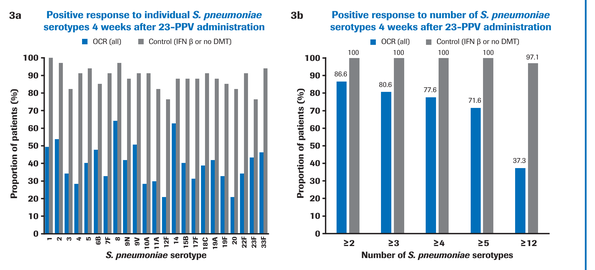


Positive response defined as a 4-fold increase in antibody titres measured 8 weeks after vaccination compared with pre-vaccination levels (pre-vaccination titre level ≥0.1 IU/mL) or an antibody titre ≥0.2 IU/mL if pre-vaccination titre was <0.1 IU/mL.
DMT, disease-modifying therapy; IFN, interferon; IgG, immunoglobulin G; OCR, ocrelizumab.

Response (IgG) to Pneumococcal Vaccine

- Serotype specific geometric mean antibody levels at 4 and 8 weeks post-vaccination were lower in OCR recipients, including those receiving the 13-PCV booster 4 weeks after 23-PPV (Group OCR1), versus those in the Control group
- Post-vaccination positive responses to individual *Streptococcus pneumoniae* serotypes in 23-PPV were lower in the OCR group versus the Control group (4 weeks, –62.8% to –25.5%; **Figure 3a**)
- The 13-PCV booster administered 4 weeks after 23-PPV in the OCR1 group did not markedly enhance the response to the 12 serotypes in common with 23-PPV (data not shown)

Figure 3. Response (IgG) to pneumococcal vaccine



Positive response: 2-fold increase or a >1 µg/mL rise in titre level (IgG), compared with pre-vaccination levels.
23-PPV, 23-valent pneumococcal polysaccharide vaccine; DMT, disease-modifying therapy; IFN, interferon; IgG; immunoglobulin G; OCR, ocrelizumab.

- The proportion of positive responders in the OCR group decreased with each increase in number of serotypes (**Figure 3b**)

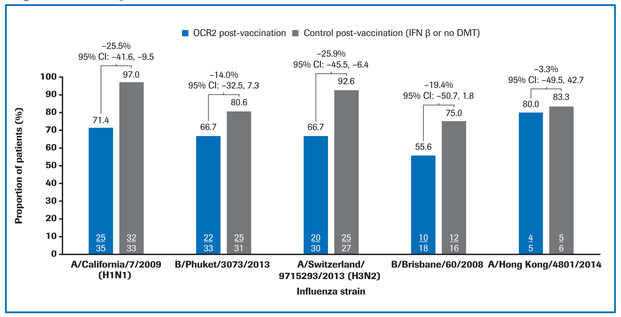
Seroprotection to Individual Influenza Strains

- The proportion of patients with seroprotective haemagglutination inhibition titres immediately prior to vaccination was higher in patients in the OCR2 group, compared with those in the Control group
- Seroprotective titres 4 weeks post-vaccination against five influenza strains (in influenza vaccines of seasons 2015/2016 and 2016/2017) ranged from 55.6% to 80.0% in patients receiving OCR and 75.0% to 97.0% in Control patients (**Figure 4**)

IgM and IgG Responses to Keyhole Limpet Haemocyanin Neoantigen

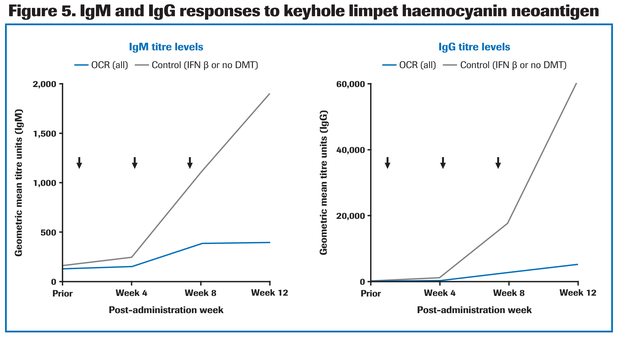
- Pre-administration geometric mean levels of IgM and IgG across treatment groups were comparable (OCR: IgM, 100 units; IgG, 274 units; Control: IgM, 130 units; IgG, 235 units)
- Post-administration responses (4, 8 and 12 weeks) were lower in OCR recipients versus Control (**Figure 5**)
  - After repeated KLH administration, a stronger boosting effect was observed in the Control group, compared with those receiving OCR

Figure 4. Seroprotection to individual influenza strains



Pre-vaccination seroprotection levels were higher in patients receiving OCR vs those in the Control group for all individual serotypes (A/California/7/2009: 54.3% vs 33.3%; B/Phuket/3073/2013: 48.5% vs 29.0%; A/Switzerland/9715293/2013: 60.0% vs 40.7%; B/Brisbane/60/2008: 50.0% vs 43.8%; A/Hong Kong/4801/2014: 20.0% vs 16.7%). Seroprotection defined as a specific haemagglutination inhibition titre >40.
DMT, disease-modifying therapy; IFN, interferon; OCR, ocrelizumab.

Figure 5. IgM and IgG responses to keyhole limpet haemocyanin neoantigen



↓ KLH administration.
DMT, disease-modifying therapy; IFN, interferon; IgG; immunoglobulin G; IgM, immunoglobulin M; KLH, keyhole limpet haemocyanin; OCR, ocrelizumab.

Safety

- The overall safety profile of OCR was consistent with pooled Phase III safety data[1,7]
- No new safety signals were identified; no serious adverse event or adverse event leading to withdrawal from treatment was reported during the ISP
- Safety findings from the VELOCE study are presented as part of a combined OCR safety report in **ePresentation EPR1105** (Hauser SL, *et al.*)

CONCLUSIONS

- Data from the Phase III OPERA I and OPERA II studies show that pre-existing humoral immunity is not affected by ocrelizumab treatment[6]
- In the VELOCE study, humoral responses were attenuated at all time points in patients who were B-cell depleted having received ocrelizumab, compared with those who did not
- Patients were nonetheless able to mount humoral responses to the vaccines and neoantigen studied
  - Cellular immune responses were not assessed
- These data confirm the current prescribing recommendations for vaccinations
  - Administer all vaccinations according to guidelines at least 6 weeks prior to initiation of ocrelizumab
- Patients should still receive seasonal influenza vaccinations since a potentially protective humoral response, even if attenuated, can be expected

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DISCLOSURES

D Stokmaier is an employee of F. Hoffmann-La Roche Ltd. K Winthrop is a consultant for GlaxoSmithKline plc, F. Hoffmann-La Roche Ltd and Pfizer Inc. C Chognot is an employee of F. Hoffmann-La Roche Ltd. J Evershed is an employee of F. Hoffmann-La Roche Ltd. M Manfrini is an employee of F. Hoffmann-La Roche Ltd. J McNamara is an employee of John McNamara Consulting Ltd.
A Bar-Or has served on scientific advisory boards for Biogen, F. Hoffmann-La Roche Ltd and Genentech, Inc., GlaxoSmithKline, Guthy-Jackson/GGF, MedImmune, Merck/EMD Serono, Mitsubishi Tanabe, Ono, Receptos and Sanofi Genzyme, and has received research support from Biogen, Novartis and Sanofi Genzyme.

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