Effect of Ocrelizumab on Vaccine Responses in Patients With Multiple Sclerosis

D Stokmaier,1 K Winthrop,2 C Chognot,1 J Evershed,1 M Manfrini,1 J McNamara,4 A Bar-Or5

1F. Hoffmann-La Roche Ltd, Basel, Switzerland; 2Division of Infectious Diseases, OHSU, Portland, OR, USA; 3Roche Products Ltd, Welwyn Garden City, UK; 4John McNamara Consulting Limited, Cambridge, UK; 5Department of Neurology and Center for NeuroInflammation and Experimental Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

BACKGROUND

Ocrelizumab (OCR) is a high-affinity treatment approved for relapsing multiple sclerosis (RMS) and is the first approved treatment for primary progressive multiple sclerosis (PPMS).

- OCR selectively depletes CD20+ B cells while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity.1

- 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.2

- There is a need to further understand the impact of OCR on the responses 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.

METHODS

Study Endpoints

- Primary endpoint: proportion of patients with a positive response (immunoglobulin G [IgG] ≥0.1 IU/mL) 4 and 8 weeks after vaccination to selected vaccines.

- Secondary endpoints included:
  - 23-valent pneumococcal polysaccharide vaccine (23-PPV) and 13-valent pneumococcal conjugate vaccine (13-PCV) - proportion of patients with a positive response against an individual pneumococcal serotype 6 weeks after vaccination.
  - Influenza vaccine: proportion of patients treated with OCR who achieved seroprotection 4 weeks after immunisation.
  - Keyhole limpet haemocyanin (KLH): proportion of anti-KLH IgG and IgM in all patients during the immunisation study period (baseline and prior to 96 weeks).

Study Design

- VELOCE is a five-period study, which includes screening, immunisation, optional OCR administration (VELOCE 1), and post-vaccination follow-up until Week 12 (Figure 1).

- Patients were randomized to receive either OCR (200 mg) or control therapy (IFN β-1a or no DMT) at baseline, and were maintained throughout the 96-week double-blind treatment period.

- The proportion of patients with seroprotective haemagglutination inhibition titres immediately post-vaccination was lower in OCR recipients versus those in the Control group (4 weeks, –16.7% to –56.0%; 8 weeks, –20.2% to –48.5%; Figure 3a).

- The proportion of positive responders in the OCR group decreased with each increase in serotype (Figure 3b).

- The proportion of patients with positive responses to individual serotypes 4 weeks after 23-PPV administration was lower in the OCR group versus the Control group (4 weeks, –62.8% to –25.5%; Figure 3c).

- The 13-PCV booster administered 4 weeks after 23-PPV in the OCR1 group did not markedly increase the proportion of positive responders to the 12 serotypes in common with 23-PPV (data not shown).

RESULTS

Table 2. Baseline demographic and disease characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (IFN β or no DMT)</th>
<th>OCR (200 mg at DMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>41.7 (5.5)</td>
<td>41.4 (7.0)</td>
</tr>
<tr>
<td>Female, %</td>
<td>60.2 (21)</td>
<td>27.0 (5.4)</td>
</tr>
<tr>
<td>Duration since MS symptom onset, years, mean (SD)</td>
<td>10.4 (6.8)</td>
<td>10.6 (9.4)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.3 (7.7)</td>
<td>26.0 (5.7)</td>
</tr>
<tr>
<td>Duration since MS diagnosis, years, mean (SD)</td>
<td>6.8 (7.0)</td>
<td>6.4 (5.4)</td>
</tr>
<tr>
<td>Duration since 1st DMT, years, mean (SD)</td>
<td>6.4 (4.0)</td>
<td>7.1 (1.2)</td>
</tr>
<tr>
<td>Days 23-PPV, mean (SD)</td>
<td>27.7 (11.9)</td>
<td>31.8 (17.6)</td>
</tr>
<tr>
<td>Number of T1 galactocerebroside, mean (SD)</td>
<td>2.8 (1.3)</td>
<td>2.8 (1.2)</td>
</tr>
<tr>
<td>Number of T2 lesions, mean (SD)</td>
<td>57.6 (45.7)</td>
<td>65.0 (28.4)</td>
</tr>
<tr>
<td>T2 lesions volume, cm³, mean (SD)</td>
<td>10.6 (13.3)</td>
<td>7.2 (6.2)</td>
</tr>
</tbody>
</table>

Safety

- The overall safety profile of OCR was consistent with pooled Phase III safety data.1

- No new safety signals were identified; no serious adverse events or adverse event leading to withdrawal from treatment were reported during the study.

- Safety findings from the VELOCE study are presented as part of a combined OCR safety report: ePresentation EPR1105 (Haser 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.1

- 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 were not.

- Patients were nonselective able to mount humoral responses to the vaccines and maintain protective titres.

- Cellular immune responses were not assessed.

- These data confirm the current prescription recommendations for vaccinations:
- Administer all vaccinations according to guidelines of the 15 time points prior to initiation of ocrelizumab.
- Patients should select seasonal influenza vaccines since a potentially protective humoral response, even if attenuated, can be expected.

ACKNOWLEDGMENTS
