Effect of Ocrelizumab on Vaccine Responses in Patients With Multiple Sclerosis

D Stokmaier, K Winthrop, C Chognot, J Evershed, M Manfrini, J McNamara, A Bar-Or

BACKGROUND
• Ocrelizumab (OCR) is a high-efficiency treatment approved for relapsing-remitting multiple sclerosis (MS) and is the first approved treatment for primary progressive multiple sclerosis
• OCR selectively depletes CD8⁺ B cells while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity

In the Phase III OPERA1 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

There is a need to further understand the impact of OCR on the response to vaccines

OBJECTIVE
• VELOCE (NCT03468401) is a Phase IIb study being conducted in the USA and Canada to evaluate the impact of OCR on humoral responses to selected vaccines (Table 1) in patients with RMS

Table 1. Vaccines and neoantigens used in VELOCE

VELOCIE vaccines/neoantigen Response pathway

23-valent pneumococcal polysaccharide vaccine

Seasonal influenza (inactivated)

23-PPV

TT

VELOCE vaccines/neoantigen Response pathway

KLH

Neutralization endpoint

Table 2. Baseline demographic and disease characteristics

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METHODS
Study Endpoints
• Primary endpoint: proportion of patients with a positive response to the tetanus toxoid (TT) containing vaccine 4 weeks after TT booster vaccination administration
– Assessed at 1 week, 4 weeks and 8 weeks after TT vaccination as a secondary endpoint

Secondary endpoints included:
– 23-valent pneumococcal polysaccharide vaccine (23-PPV) and 13-valent pneumococal 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 in 4 weeks post-vaccination compared with patients in the Control group

Keyhole Limpet Hemocyanin (KLH) neoantigen: all patients were vaccinated during the immunization study period (ISP); independently prior to and 4, 8 and 12 weeks after the last administration of KLH

Study Design
VELOCIE has a study period, which includes screening, immunization, optional OCR extension, safety follow-up, and extended B-cell monitoring

Patients were randomized (1:1) to receive one dose of OCR 500 mg (per mg serologic information), or remain on IFN β-1a or no disease-modifying therapy (DMDT). Control (DMDT) group was either continued or switched to OCR

Patients in the DMDT group were assigned to OCR or IFN β-1a at randomization

Vaccinations in the Control group were started at Week 12 when 8 weeks of 23-PPV had been delivered

Inclusion/Exclusion Criteria
• Patients were aged 18-65 years (inclusive) at diagnosis of MS (McDonald Criteria, 2010) and a baseline Expanded Disability Status Scale score at screening of 0-6.5

• Relapsing-remitting in combination with 7-10 years prior to screening
• Relapsing-remitting or secondary progressive MS

• Patients were excluded if they had received any immunomodulators <3 years prior to screening

• Patients were excluded if they had received any pneumococcus ≥3 years prior to screening at a dose level ≥30 mg prior to randomization, or had previous exposure to KLH

Analysis Population
• We report findings from the Observed Cases population (all patients completing the ISP during the OSP) for patients not receiving OCR at the end of the ISP (last patient, last visit on March 19, 2018 (planned clinical cut-off date))

• There was a formal assessment of non-inferiority, comparability and SIMC/TOXUO with the following nomogram method

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. M Manfrini is an employee of F. Hoffmann-La Roche Ltd. J McNamara is an employee of John McNamara Consulting Ltd.

RESULTS
Baseline Demographic and Disease Characteristics

The mean number of T1 gadolinium-enhancing lesions at baseline was higher in patients in the Control group compared with those in the OCR group

After repeated KLH administration, a stronger boosting effect was observed in the Control group, compared with those receiving OCR

Patients had received ≥1 vaccination with a TT-containing vaccine >2 years prior to screening

• 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 Control group than in the OCR group

• Twelve patients (35%) randomized to the Control group remained on IFN β during the ISP

• The proportion of positive responders in the OCR group decreased with each increase in number of vaccinations received.

Table 2. Baseline demographic and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (IFN β or no DMT)</th>
<th>OCR (all)</th>
<th>OCR1</th>
<th>OCR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>52.7 (9.4)</td>
<td>51.9 (10.1)</td>
<td>52.8 (9.5)</td>
<td>52.0 (10.7)</td>
</tr>
<tr>
<td>Duration since MS symptom onset, years, mean (SD)</td>
<td>14.4 (10.1)</td>
<td>14.3 (10.1)</td>
<td>13.7 (9.9)</td>
<td>14.2 (11.1)</td>
</tr>
<tr>
<td>Caucasian, n (%):</td>
<td>45 (88.2)</td>
<td>44 (91.7)</td>
<td>40 (90.0)</td>
<td>43 (90.3)</td>
</tr>
<tr>
<td>Female, n (%):</td>
<td>6 (9.4)</td>
<td>6 (12.5)</td>
<td>5 (11.4)</td>
<td>5 (10.2)</td>
</tr>
<tr>
<td>Baseline EDSS score, mean (SD)</td>
<td>3.7 (0.6)</td>
<td>3.5 (0.5)</td>
<td>3.4 (0.5)</td>
<td>3.5 (0.5)</td>
</tr>
<tr>
<td>Patients had received ≥1 vaccination with a TT-containing vaccine &gt;2 years prior to screening</td>
<td>1 (1.9)</td>
<td>1 (1.9)</td>
<td>1 (2.4)</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

Figure 1. VELOCIE study design

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

Figure 3. Response (IgG) to pneumococcal vaccine

Figure 4. Seroprotection to individual influenza strain

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

CONCLUSIONS
• Data from the Phase III OPERA1 and OPERA II studies show that pre-existing humoral immunity is not affected by disease-modifying treatment

In the VELOCE study, humoral responses were assessed 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 neoantigens studied

ACROGNOMIES
• The overall safety profile of OCR was consistent with published Phase III safety data
• No serious 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 inPoster DS05 (Evershed SL, et al)

REFERENCES

D Stokmaier, K Winthrop, C Chognot, J Evershed, M Manfrini, J McNamara, A Bar-Or

Presented at the 2018 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC); May 30–June 2, 2018; Nashville, TN, USA

Poster DX43

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