Serum Immunoglobulin Levels and Risk of Serious Infections in the Pivotal Phase III Trials of Ocrelizumab in Multiple Sclerosis and Their Open-Label Extensions

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Disclosures

**Tobias Derfuss** has served on scientific advisory boards, steering committees and data safety monitoring boards for Actelion, Biogen, Celgene, Genzyme, GeNeuro, Merck, Mitsubishi Pharma, Novartis, Roche, Octapharma and MedDay; has received travel and/or speaker honoraria from Biogen, Genzyme, Merck, Novartis, Roche and Merck Serono; and has received research support from Biogen, Novartis, the Swiss MS Society and the Swiss National Foundation.

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**Richard Hughes** is an employee and shareholder of F. Hoffmann-La Roche Ltd.

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**Annette Sauter** is an employee and shareholder of F. Hoffmann-La Roche Ltd.

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**Stephen L Hauser** serves on the board of trustees for Neurona and on scientific advisory boards for Alector, Annexon, Bionure, Molecular Stethoscope, and SymBiotix; and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

**Amit Bar-Or** has received consulting fees from Actelion, Atara Biotherapeutics, Biogen Idec, Brainstorm Celgene/Receptos, Genentech, Inc., GlaxoSmithKline, F. Hoffmann-La Roche Ltd, MAPI, MedImmune, Merck/EMD Serono, Novartis, and Sanofi-Genzyme; has carried out contracted research for Genentech, Inc., and Biogen; and receives a salary from The University of Pennsylvania, Perelman School of Medicine.

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Background: Infections in MS and rates of serious infections with ocrelizumab

- Patients with MS have a higher risk of infections and of hospital admission rates for infection compared with the general population\(^1\)

\[^1\] Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase III OPERA and ORATORIO studies. CI, confidence interval; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label ocrelizumab; PY, patient years.

**Background: Infections in MS and rates of serious infections with ocrelizumab**

- Patients with MS have a higher risk of infections and of hospital admission rates for infection compared with the general population.¹
- In ocrelizumab MS clinical trials, infections were one of the most frequently reported adverse events.
  - In Phase III trials, rates of SIs were low, and no increased risk vs IFN β-1a and placebo was observed; rates of SIs remain low at 6-year follow-up.

![Graph showing infection-related hospitalisations per 100 PY (95% CI) for MS registries, OPERA, ORATORIO, and Phase III all exposure](image)

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¹Includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase III OPERA and ORATORIO studies.

CI, confidence interval; DBP, double-blind period; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient years; SI, serious infection.

Objective

- The risk of serious infections in patients with MS is influenced by diverse factors such as age, body mass index, comorbidities, disability level, concomitant treatments, neutrophil and lymphocyte count\(^1\)–\(^3\)

- Immunoglobulins also play a major role in adaptive immunity and the risk of certain types of infection is increased when immunoglobulin levels are low\(^4\)

- Reduced blood concentration of IgG, IgM, and/or IgA is known to occur in patients treated with B-cell–depleting therapy (secondary antibody deficiency), including ocrelizumab\(^5\)–\(^10\)

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**Objective:** To assess serum immunoglobulin levels over 6 years (288 weeks) in OPERA and ORATORIO and evaluate a potential association between a decrease in IgG, IgM or IgA levels and serious infections

Ig, immunoglobulin; MS, multiple sclerosis.

10. Ocrevus 300 mg concentrate for solution for infusion (Summary of Product Characteristics; 26 June 2019).
Methods: OPERA I/II and ORATORIO study designs

• Serum Ig levels were measured at least every 24 weeks during the DBP and OLE periods.

Serum Ig measurement
BL, baseline; DBP, double-blind period; IFN, interferon; Ig, immunoglobulin; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous.
Methods: Counting serious infections during periods of Ig above vs below LLN

Illustrative example

<table>
<thead>
<tr>
<th>IgM</th>
<th>0.4 g/L (40 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>5.65 g/L (565 mg/dL)</td>
</tr>
<tr>
<td>IgA</td>
<td>0.7 g/L (70 mg/dL)</td>
</tr>
</tbody>
</table>

**Ig, immunoglobulin; LLN, lower limit of normal; SI, serious infection; ULN, upper limit of normal.**
Results
Over 6 years of OCR treatment, a mean absolute reduction in serum IgM levels of ~0.78 g/L (mean relative reduction of 55.4%) in OPERA and ~0.77 g/L (mean relative reduction of 53.7%) in ORATORIO was observed.

OCR treatment is associated with a faster drop in serum IgM in the first year followed by a slower decline.
Within the first 6 years (288 weeks), treatment with OCR reduces serum IgG concentration at an average rate of \(-0.32\) g/L per year \((-3.0\%\) per year). The trajectory for change in IgA levels over time was similar to IgG.
Proportion of patients with Ig levels <LLN

For the majority of patients with either RMS or PPMS, serum immunoglobulin levels remain above LLN at approximately 6 years (288 weeks) of exposure.

January 2019 data cut, OPERA and ORATORIO all-exposure population.
BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.
Rates of SIs per 100 PY during IgG, IgM, and IgA values <LLN vs ≥LLN

- **Phase III all exposure**
  - IgM: 3.54 (95% CI: 2.24 - 2.21)
  - IgG: 5.48 (95% CI: 1.89 - 2.14)
  - IgA: 2.74 (95% CI: 2.21 - 2.21)

**Table**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>IgM &lt;LLN</th>
<th>IgM ≥LLN</th>
<th>IgG &lt;LLN</th>
<th>IgG ≥LLN</th>
<th>IgA &lt;LLN</th>
<th>IgA ≥LLN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,092</td>
<td>729</td>
<td>1,383</td>
<td>152</td>
<td>1,940</td>
<td>127</td>
<td>1965</td>
</tr>
<tr>
<td>Episodes (n)</td>
<td>-</td>
<td>929</td>
<td>2,368</td>
<td>288</td>
<td>2,269</td>
<td>166</td>
</tr>
<tr>
<td>PY</td>
<td>9,891</td>
<td>2,003</td>
<td>7,989</td>
<td>255</td>
<td>9,737</td>
<td>256</td>
</tr>
<tr>
<td>No. of SIs</td>
<td>222</td>
<td>71</td>
<td>151</td>
<td>14</td>
<td>208</td>
<td>7</td>
</tr>
</tbody>
</table>

January 2019 data cut. Serious infections are defined using adverse events falling into the MedDRA System Organ Class ‘Infections and Infestations’ and using ‘Is the event non-serious or serious’ from the adverse events CRF page; includes patients who received any dose of OCR during the controlled treatment and associated OLE periods of the Phase III OPERA and ORATORIO studies. Multiple occurrences of the same adverse event in one individual are counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution. Exposure of <LLN is counted from the day lab <LLN until the day lab ≥LLN; exposure gap is excluded from PY. CI, confidence interval; CRF, case report form; Ig, immunoglobulin; LLN, lower limit of normal; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PY, patient years; SI, serious infection.
Characteristics and outcomes of SIs associated with low Ig levels

- Urinary tract infections, cellulitis and pneumonia were the most common serious infections associated with Ig levels <LLN
  - This is similar to overall SIs in patients with MS treated with ocrelizumab
  - This is also consistent with types of serious infections observed in MS registries\textsuperscript{1–3}

- Most SIs associated with Ig levels <LLN:
  - Were of Grade 3 (69.1%). No fatal outcomes or opportunistic infections were observed
  - Resolved without sequelae (92.6%), within the expected clinical course (78.5% lasted <28 days) by using standard-of-care treatment
  - Resulted in no action taken (dose not changed) with ocrelizumab (87.7%)

January 2019 data cut. Pooled OPERA and ORATORIO all-exposure population.
Ig, immunoglobulin; LLN, lower limit of normal; MS, multiple sclerosis; SI, serious infection.
Conclusions

At approximately 6 study years (288 weeks) of ocrelizumab exposure:

1. Rates of serious infections remain low and consistent with rates of infection-related hospitalisations in real-world MS cohorts

2. A reduction in serum Ig levels is observed, at an approximate mean rate of 3–4% per year for IgG, but for the majority of patients Ig levels remain above LLN

3. There is an apparent association between decreased levels of IgG (and less so for IgM or IgA) and serious infections, but overall incidence is low

4. The majority of serious infections following episodes of drop in Ig levels <LLN were urinary tract infections, cellulitis and pneumonia; most resolved with standard of care, and in most cases patients remained on treatment with ocrelizumab

Ig, immunoglobulin; LLN, lower limit of normal; MS, multiple sclerosis.
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