Pregnancy Outcomes in Patients Treated With Ocrelizumab

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INTRODUCTION AND PURPOSE
Ocrelizumab (OCR), a humanized monoclonal antibody that selectively targets CD20+ B-cells, is approved for the treatment of stopping forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

Results of international clinical trials indicate that—
— 4,611 patients have received OCR in clinical trials (as of 7 January 2019).
— Approximately 2,507 patients have received OCR in the post-marketing setting (as of 31 March 2018).
— Estimated patient exposure from clinical trials and the post-marketing setting are 14,200 (+37%) and 8,757 patient-years, respectively.
— A significant proportion of patients eligible for treatment with OCR will be women of reproductive age.

Mean age of treatment onset is approximately 30 years.
— Rises in the ratio of patients with RMS is approximately 3:1.
— Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, revealed dose toxicity and embryo-fetal development.

RESULTS

Overall Patient Exposure
As of 31 March 2019, 362 pregnancies exposed to OCR have been reported (Figure 1).

Figure 1. Overview of cumulative maternal exposure pregnancies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposed</th>
<th>Unexposed</th>
<th>Exposure in utero</th>
<th>In utero born</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>25 (25)</td>
<td>17 (36)</td>
<td>13 (14)</td>
<td>12 (23)</td>
<td>50 (43)</td>
</tr>
<tr>
<td>Still birth</td>
<td>17 (36)</td>
<td>19 (44)</td>
<td>11 (14)</td>
<td>13 (28)</td>
<td>40 (34)</td>
</tr>
<tr>
<td>Elective termination</td>
<td>17 (36)</td>
<td>3 (7)</td>
<td>2.5 (3)</td>
<td>4 (9)</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>7 (15)</td>
<td>7 (17)</td>
<td>2 (3)</td>
<td>4 (9)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>7 (15)</td>
<td>10 (25)</td>
<td>3.5 (5)</td>
<td>5 (9)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>3 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Live preterm birth with anomaly</td>
<td>3 (6)</td>
<td>2 (5)</td>
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<tr>
<td>Unexposed</td>
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<td>28 (62)</td>
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For a summary of clinical data, please scan here

• Studies on the effect of OCR on human reproduction and neonatal B-cell function have not been performed.
• Transient peripheral B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

• A previously reported case of an EOS clinical trial includes indications (RMS, PPMS, rhematoid arthritis and systemic lupus erythematosus).

• The database records information from all sources.

• No abnormalities reported; no infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

• Ocrelizumab, such as OCR, do not cause the patients during the first trimester of pregnancy (3 months). OCR transfer is assumed to occur only after the 16th week of gestation, and therefore the fetus is protected from exposure during organogenesis.

Box 1. Rationale for use of contraception during and after OCR treatment

• Effective contraception should be used while receiving OCR and for the period of time recommended by regulatory bodies following the last infusion of OCR to provide for appropriate drug elimination variability.

• Intensified drug-elimination variability — First-order elimination processes are near-complete (>90%) after five half-lives — Rapid elimination in patients with RMS is approximately 26 days — Near-complete elimination in patients with RMS and an average T1/2 is approximately 10 weeks/4.5 months — Near-complete elimination in patient with the longest T1/2 seen in female patients with RMS (51 days) is approximately 50 weeks/9 months: OCR transfer is assumed to occur only after the 16th week of gestation, and therefore the fetus is protected from exposure during organogenesis.

• There were three cases of infants exposed to OCR via lactation:

1. Thirteen pregnancies (12 with foetal exposure) resulted in live births
2. Seven pregnancies resulted in live births (data available; six cases may be duplicate cases from Phase III studies)
3. Ten pregnancies (9 with foetal exposure) resulted in spontaneous abortions

Infant Exposure Through Lactation (as of 31 March 2019)

• There were three cases of infants exposed to OCR via lactation:

1. Two infants were exposed only post partum and had slight B-cell decrease at 3 months of age that were not consistent with true B-cell depletion in terms of level of depletion or rate of return to normal range (1 week).

CONCLUSIONS

• Reviewed cases are suggestive of an ocrelizumab-related increased risk of adverse pregnancy/birth outcomes.

OBJECTIVE
To report pregnancy, birth, neonatal and infant outcomes in female patients who became pregnant or who were breastfeeding during OCR trials and post-marketing analyses in multiple sclerosis (MS) up to 31 March 2019.

In total: 62 reported live births (30%) resulted in a healthy baby.

• An overview of outcomes of live births to mothers with MS including births with abnormal outcomes are presented in Figure 2.

Pregnancy Exposure in Patients With MS

Outcomes of the 287 maternal exposure pregnancies in patients with MS are shown in Table 1.

Table 1. Outcomes of maternal exposure pregnancies in patients with MS

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METHODS

Study Design
The analysis includes OCR-exposed women with MS recorded from clinical trials and post-marketing experience of OCR.

The database records information from all sources and includes:
— Clinical trials: all pregnancy cases (including nomenclature reports) and all cases with serious adverse events where OCR is considered ‘suspect’
— Spontaneous reports: all cases (serious and nonserious) where OCR is considered ‘suspect’
— Pregnancy outcomes, including information about child birth up to 1 year after birth.

Consortium: genitourinary, neonatal and Children, low birth weight and high birth weight

• One birth of an infant with a heart defect and neonatal/infantile platelet count and concurrent urino tract infection

— No further information provided.

ACKNOWLEDGMENTS

REFERENCES

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