An Update on Pregnancy Outcomes Following Ocrelizumab Treatment in Patients With Multiple Sclerosis and Other Autoimmune Diseases

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BACKGROUND

- Ocrelizumab (OCR), a humanized monoclonal antibody that selectively targets CD20$^+$ B cells, is approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS)[1]
- The demographic profile of patients with multiple sclerosis (MS), including a mean age of onset of approximately 30 years and a female-to-male ratio of approximately 3:1,[2] indicates that a significant proportion of patients eligible for treatment with OCR will be women of reproductive age
- Immunoglobulin molecules such as OCR do not cross the placenta during the first trimester of pregnancy,[3] but transfer of OCR can occur thereafter and may cause fetal CD20$^+$ B-cell depletion[1,4]
- The US OCR prescribing information states, 'Women of childbearing potential should use contraception while receiving OCR and for 6 months after the last infusion of OCR'[1]
- The rationale for this statement is described in **Box 1**

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

- Average $t_{1/2}$ of OCR in RMS: 26 days[1]
- Elimination after last OCR administration
  - Based on $t_{1/2}$ 26 days:
    - Five $t_{1/2}$ ≙130 days ≙ 19 weeks ≙ **4.5 months**[a]
  - Taking into account interpatient variability:
    - Longest $t_{1/2}$ in female patients with RMS: 53 days[4]
    - Five $t_{1/2}$ ≙ 266 days ≙ 38 weeks ≙ **9 months**
- Effective contraception should be used while receiving OCR and for **6 months** after the last infusion of OCR[1] to provide for interpatient drug-elimination variability[b]
  - IgG1 antibodies do **not** cross placenta during first trimester of pregnancy (3 months)[3]
  - OCR transfer is assumed to occur only after 16th week of gestation, and therefore the fetus is protected from exposure during organogenesis[3,5]

[a]First-order processes, such as elimination, are near-complete after 4–5 half-lives;[4] [b]Recommendations for the duration of effective contraception may vary for different health authorities.
IgG1, immunoglobulin G1; OCR, ocrelizumab; RMS, relapsing multiple sclerosis; $t_{1/2}$, terminal half-life.

- In an embryo-fetal developmental study in pregnant cynomolgus monkeys, intravenous (IV) administration of OCR (loading doses of 15 or 75 mg/kg on gestation days 20, 21 and 22, followed by weekly doses of 20 or 100 mg/kg) during the organogenesis period resulted in no evidence of maternal toxicity, embryotoxicity or teratogenicity and no observed effect on abortion or embryo-fetal fatality rate[1,4]
  - OCR administration did result in B-cell depletion in both dams and offspring, with circulating B-cell populations returning to within expected limits within 6 months of birth[4]
- In a pre- and post-natal development study, IV administration of OCR (three daily loading doses of 15 or 75 mg/kg followed by weekly doses of 20 or 100 mg/kg) to pregnant monkeys throughout the period of organogenesis and continuing through the neonatal period resulted in:[1]
  - Two neonatal deaths
    - The cause of the neonatal deaths is uncertain; however, both affected fetuses were found to have bacterial infections
  - Renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow and severe decreases in circulating B cells were observed in neonates
  - Reduced testicular weight was observed in neonates at the high dose
- A dose below which adverse developmental outcomes might occur could not be established from these studies; the doses tested in monkeys were 2 and 10 times the recommended human dose of 600 mg on a mg/kg basis
- Studies of the effect of OCR on human reproduction have not been performed

OBJECTIVE

- A previous communication[7] provided an overview of pregnancy outcomes from trials in RMS,[8,9] PPMS[10] and also trials in which OCR has been studied as a treatment for rheumatoid arthritis (RA)[11–14] and systemic lupus erythematosus (SLE),[15] up to September 14, 2015
- Here, we update the assessment of the pregnancy, fetal, neonatal and infant outcomes in female patients who became pregnant during OCR trials in MS, RA and SLE up to January 31, 2017
- Pregnancy outcomes were monitored across all trials; however, only trials in which pregnancies were reported are referenced in this review
  - A summary of the study designs is presented in **Table 1**

Table 1. Study design of randomized, controlled trials in which pregnancies were reported

	Trial	N	Treatment arms	Duration	Primary endpoint
RMS	**Phase II[8] (WA21493)**	220	• Placebo IV Days 1 and 15/OCR IV 300 mg Weeks 24 and 26 • OCR IV 300 mg Days 1 and 15/OCR IV 600 mg Week 24 • OCR IV 1,000 mg Days 1 and 15/OCR IV 1,000 mg Week 24 • IFN β-1a IM (30 µg) qw/OCR IV 300 mg Weeks 24 and 26	96 weeks	Number of T1 Gd-enhancing lesions at Weeks 12, 16, 20 and 24
	OPERA I[9]	821	• OCR IV 600 mg q24w • IFN β-1a SC (44 µg) tiw	96 weeks	ARR at Week 96
	OPERA II[9]	835			
RA	**SCRIPT[14] (TNF-IR)**	836	• Placebo IV[a,b] • OCR IV 200 mg or 500 mg on Days 1 and 15 and at Weeks 24 and 26[a,b]	48 weeks	ACR20 response at Weeks 24 and 48
	STAGE[12] (MTX-IR)	1,006			
	FEATURE[11] (DMARD-IR)	312	• Placebo IV[b] • OCR IV 200 mg on Days 1 and 15[b] • OCR IV 400 mg on Day 1[b]	24 weeks	ACR20 response at Week 24
	FILM[13] (MTX-naive)	605	• Placebo IV[b] • OCR IV 200 mg or 500 mg[b] • OCR/placebo given on Days 1 and 15 and at Weeks 24/26, 52/54 and 76/78	104 weeks (terminated early)[a]	Change in modified total Sharp score at Week 104
SLE	**BELONG[15] (proliferative lupus nephritis)**	381	• Placebo IV[c] • OCR IV 400 mg or 1,000 mg on Days 1 and 15, at Week 16 and q16w[c]	96 weeks (terminated early)[a]	Renal response at Week 48

[a]In SCRIPT, all patients received concomitant leflunomide or MTX; [b]In STAGE, FEATURE and FILM, all patients received concomitant MTX; [c]In BELONG, patients received corticosteroid plus one of two immunosuppressant regimens considered standard of care: a) cyclophosphamide and azathioprine or b) mycophenolate mofetil; [d]Terminated as a result of an overall risk/benefit assessment based on the two pivotal STAGE and SCRIPT Phase III RA trials; [e]Terminated early due to an imbalance in serious infections in OCR-treated patients vs placebo-treated patients.
National Clinical Trial identifiers: Phase II (WA21493), NCT00676715; OPERA I, NCT01247324; OPERA II, NCT01412333, SCRIPT, NCT00476996; STAGE, NCT00406419; FEATURE, NCT00673920; FILM, NCT00488580; BELONG, NCT00626197.
ACR20, American College of Rheumatology 20% improvement criteria; ARR, annualized relapse rate; DMARD, disease-modifying antirheumatic drug; Gd, gadolinium; IFN, interferon; IM, intramuscular; IR, inadequate response; IV, intravenous; MTX, methotrexate; OCR, ocrelizumab; qw, weekly; q16w, every 16 weeks; q24w, every 24 weeks; RA, rheumatoid arthritis; RMS, relapsing multiple sclerosis; SC, subcutaneous; SLE, systemic lupus erythematosus; tiw, three times weekly; TNF, tumor necrosis factor.

METHODS

Study Design

- This analysis included OCR-exposed women in clinical trials of OCR in patients with MS, RA or SLE in which OCR doses ranged from 20 to 2,000 mg
- Information on contraception and pregnancy provided to patients enrolling in OCR clinical trials is summarized in **Box 2**
- As part of the inclusion criteria for all OCR trials, female patients of childbearing potential must have had a negative urine pregnancy test, while pregnancy and/or lactation were part of the exclusion criteria
- Across trials, women of childbearing potential were required to use two methods of contraception and continue contraception for 1 year/48 weeks after the last OCR infusion or until B cells were repleted, whichever was longer
- Urine pregnancy tests were performed at all infusion visits; if positive, dosing was stopped and the result was confirmed with a serum pregnancy test
- Maternal exposure was defined as receiving at least one OCR infusion at any time point before conception and/or during the pregnancy
- Based on the average terminal half-life ($t_{1/2}$) of OCR and absence of relevant transplacental transfer of immunoglobulins during the first trimester (see **Box 1**), an embryo/fetus was considered exposed to OCR *in utero* if the last infusion occurred within 3 months of conception or during pregnancy or if the date of infusion was unknown
- All pregnancies occurring during the studies were followed to determine outcomes

Box 2. Pregnancy-related information provided to patients in clinical trials of MS, RA and SLE

Contraception	Female patients should take all appropriate precautions to avoid becoming pregnant during this study and for the entire duration of B-cell depletion. Women of childbearing potential should use adequate contraception for the duration of the trial and for 1 year after receiving their last infusion of ocrelizumab, whichever is the longer.
Pregnancy tests	All women of childbearing potential will have regular pregnancy tests.
Withdrawal from study	A female patient must be instructed to immediately inform the investigator if she becomes pregnant; if pregnancy is confirmed the patient is withdrawn from treatment.

RESULTS

Key Baseline Demographics

- Key baseline demographics of patients enrolled in MS, RA and SLE trials are summarized in **Table 2**

Table 2. Baseline demographics of patients enrolled in OCR MS, RA and SLE clinical trials

	MS[a]	RA[b]	SLE[c]
N	2,147	2,926	332
Female, %	61.9	80.0	87.1
Mean age (range), years	39.5 (18–58)	52.6 (18–90)	31.1 (16–69)
Mean age at conception, years[d]	31.4	30.8	28.0

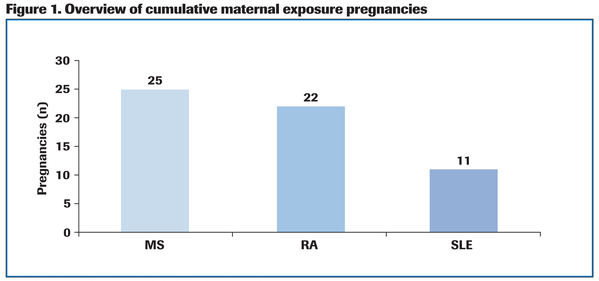
[a]All patients exposed to OCR in the Phase II, OPERA I, OPERA II and ORATORIO clinical trials; [b]All patients exposed to OCR in the STAGE, SCRIPT, FEATURE and FILM clinical trials; [c]Total randomized population in the BELONG trial; [d]Age was available for 57 of the 58 (MS: 24/25; RA: 22/22: SLE: 11/11) pregnancies reported up to January 31, 2017 and ranged from 17 to 42 years.
MS, multiple sclerosis; OCR, ocrelizumab; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Overview of Maternal Exposure Pregnancies by Indication

- From 2008 to January 31, 2017, 56 women enrolled in OCR studies reported 58 pregnancies (**Figure 1**)
  - One patient with lupus nephritis had two consecutive pregnancies, each resulting in the birth of a healthy baby at term
  - One patient with RA experienced two consecutive spontaneous abortions[a]

[a]In a study by Kaplan et al., the rate of spontaneous abortion in 96 women with RA was higher versus a control group with osteoarthritis (rate of spontaneous abortions per number of total pregnancies 25.1% versus 16.6%).[16]

Figure 1. Overview of cumulative maternal exposure pregnancies

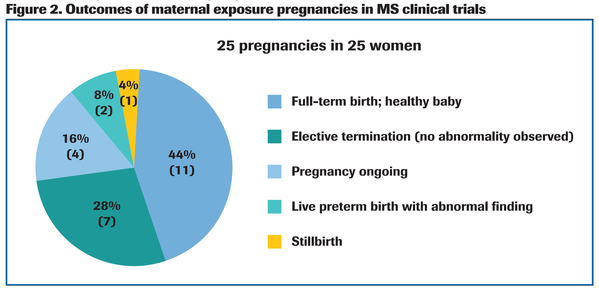


MS, multiple sclerosis; RA rheumatoid arthritis; SLE, systemic lupus erythematosus.

Maternal Exposure Pregnancies in MS Clinical Trials to January 2017

- There were 25 maternal exposure pregnancies up to January 31, 2017 (**Figure 2**)
  - Eleven full-term, healthy newborns
  - Two live preterm births with an abnormal finding
    - In the first case born at 34 weeks' gestation, there were findings of benign nasopharyngeal neoplasm (histopathological details unknown), jaundice, respiratory distress and low birth weight
      - The last infusion of OCR was 23 weeks prior to last menstrual period (≈6 months prior to conception); the embryo/fetus was not exposed to OCR *in utero*
    - The second case was delivered by cesarean section due to pre-eclampsia after 32 weeks of pregnancy
      - Temperature instability, feeding difficulties, bradycardia, respiratory distress and anemia were reported, but no congenital anomalies were observed
      - As the last OCR infusion was administered ≈10 weeks before conception, the embryo/fetus is considered exposed to OCR *in utero*; however, the preterm birth is assessed as unrelated to OCR and related to pre-eclampsia
  - Seven elective terminations of pregnancy
    - No abnormalities were reported in embryos or products of conception
  - One stillbirth at unknown gestational week
    - The embryo/fetus was considered exposed to OCR as the estimated gestational age (based on fetal weight and height) was ≈7–8 months, indicating that the pregnancy could have started ≈1.5–3.5 months before the last OCR dose and ≈2–4 months after the penultimate OCR dose
  - Four pregnancies were ongoing at the time of report

Figure 2. Outcomes of maternal exposure pregnancies in MS clinical trials



Pregnancy Outcomes in the MS Clinical Trials

Pregnancies Considered to Have Fetal OCR Exposure

- Among 14 pregnancies as of January 31, 2017, the outcomes were:
  - Four pregnancies resulted in a healthy term baby
  - Six pregnancies resulted in elective terminations, including two therapeutic abortions for which the reason for termination was not reported
  - One preterm infant (32 weeks' gestation) due to pre-eclampsia leading to a cesarean section with temperature instability, feeding difficulties, bradycardia, respiratory distress and anemia
  - One stillbirth at unknown gestational age
  - Two pregnancies ongoing at the time of report

Pregnancies Considered *Not* to Have Fetal OCR Exposure

- Among 11 pregnancies as of January 31, 2017, the outcomes were:
  - Seven healthy term babies
  - One preterm infant (34 weeks' gestation) with benign nasopharyngeal neoplasm, jaundice, respiratory disease and low birth weight
  - One elective termination
  - Two pregnancies ongoing at the time of report

Maternal Exposure Pregnancies in RA and SLE Clinical Trials

There were 33 maternal exposure pregnancies in 31 patients with RA or SLE as of January 31, 2017:

- Eleven pregnancies resulted in healthy term babies (two reported for one mother)
- One pregnancy resulted in a healthy baby born at an unknown gestational week
- Seven pregnancies resulted in live births with abnormal findings (structural malformation, functional deficit, growth abnormality) and/or preterm birth[a]
- Two pregnancies resulted in elective termination
- Ten pregnancies in nine women resulted in spontaneous abortion (one patient experienced a spontaneous abortion on two occasions), missed abortion or anembryonic pregnancy[b]
- One pregnancy resulted in fetal death at 7.5 months' gestation secondary to fatal pulmonary embolism of mother
- One pregnancy was lost to follow-up

[a]All patients received past or concomitant methotrexate, mycophenolate mofetil, hydroxychloroquine sulfate or azathioprine. In two of these seven pregnancies (both patients with RA), preterm birth was the only abnormality reported; [b]Eight of the spontaneous abortions occurred in seven patients with RA (one patient experienced a spontaneous abortion on two occasions), all of whom were receiving concomitant methotrexate treatment.

CONCLUSIONS

- B-cell levels in neonates following maternal exposure to ocrelizumab have not been studied in clinical trials; however, transient peripheral B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to other anti-CD20$^+$ antibodies during pregnancy
- As a large proportion of patients with MS are women of reproductive age and as the knowledge on the effect of ocrelizumab on the immune system is incomplete, pregnancy outcomes in patients exposed to ocrelizumab are important to understand
- Although this report covering the period up to January 31, 2017 extends the knowledge on pregnancy outcomes from the ocrelizumab clinical development program, the number of pregnancies remains small, limiting the ability to draw conclusions
- Pregnancy outcomes, including information about child health up to 1 year after birth, will be collected in ongoing ocrelizumab studies and post-marketing experience will continue to be collected and assessed
- Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab[1]

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