Pregnancy Outcomes in Ofatumumab-treated Patients With Multiple Sclerosis

DMT35

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Background

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[1,2]
- As per the label of ofatumumab women of childbearing potential should use effective contraception during and for at least 6 months after discontinuation of ofatumumab treatment[1,2]
- Early treatment interruption upon unplanned/expected pregnancy could pose low risk of fetal exposure owing to short half-life ($t_{1/2}$) of ofatumumab of approximately 16 days[1] and an average clearance within 12 weeks (which is ~5 times greaterthan the $t_{1/2}$)
- Data on the effect of ofatumumab on pregnancy outcomes are limited in humans. Based on the current knowledge:
  - Exposure to ofatumumab during gestation did not cause maternal toxicity in cynomolgus monkeys, and no adverse effects were observed on the prenatal or postnatal development[3]
  - The maternal-fetal transfer of Immunoglobulin G (IgG) during the first trimester is minimal and fetal IgG concentration starts to rise from the second trimester[4]
  - Transient B-cell depletion and lymphocytopenia have been observed in infants whose mothers were exposed to other anti-CD20 antibodies during pregnancy[1, 5, 6]
- As of August 31, 2021, no congenital anomalies were reported in infants born to women exposed to ofatumumab during pregnancy[7]

Objective

- To report the updated (data cut-off: March 25, 2022) cumulative pregnancy outcomes in women with RMS exposed to ofatumumab during or prior to unplanned pregnancy

Methods

Data collection

- Novartis Global Safety Database was searched using following search terms: MedDRA SMQ for 'Pregnancy and neonatal topics (broad)', with a data cut-off of March 25, 2022
- Cumulative data for cases with maternal exposure, where women were exposed to ofatumumab during the pregnancy or 6 months prior to last menstrual period were analyzed
- Both prospective and retrospective cases were included in the analysis
  - A case is defined as prospective if at the time of entry (i.e., first receipt by Novartis) pregnancy outcome has not yet occurred or there is no report of an abnormal prenatal testing result (including cases where prenatal testing has not yet been performed, or cases were prenatal testing has been performed but results were either normal or not specified)
  - A case is defined as retrospective if at the time of entry (i.e., first receipt by Novartis) pregnancy outcome has already occurred or prenatal testing results were abnormal (regardless of whether pregnancy outcome has occurred)

Outcomes

- Cumulative data on pregnancy outcomes, with attention to health care professional confirmed diagnosis of fetal developmental anomalies, fetal malformation, and/or birth defects associated with ofatumumab were analyzed
- The following maternal and infant outcomes were collected from the reporting of pregnancy up to a maximum of 1 year of infant age

Pregnancy outcomes

- Live birth
- Spontaneous abortion[a]
- Therapeutic abortion[b]
- Still birth
- Elective termination

[a]Spontaneous abortion: The fetus is spontaneously aborted prior to 22 weeks' gestation; prior fetal status via prenatal testing may or may not be known

[b]Therapeutic abortion: Abortion due to abnormal fetus, fetal death, risk to the mother, or choice of mother of an otherwise normal fetus

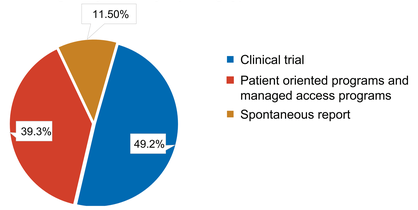
Infant outcomes

- Congenital anomalies
- Infections
- Developmental delays

Results

- As of March 25, 2022, 61 pregnancies with maternal exposure to ofatumumab were reported in the Novartis Global safety database from (**Figure 1**):
  - Clinical trial: 30 (49.2%) cases
  - Patient oriented programs and managed access programs: 24 (39.3%) cases
  - Spontaneous report: 7 (11.5%) cases
- Mean age (range): 32.8 years (19-47 years)
- Of these 61 cases,
  - A total of 52 cases were reported prospectively and 9 cases were reported retrospectively
  - Among the prospective cases, 27 cases were exposed to ofatumumab in first trimester, 2 cases were exposed in peri-LMP period and in remaining 23 cases timing is not known
  - Among the retrospective cases, 5 cases were exposed to ofatumumab in first trimester, 1 case was exposed to ofatumumab in peri-LMP period and in remaining 3 cases timing is not known
- Ofatumumab treatment was discontinued in all women following confirmation of the pregnancy

Figure 1. Pregnancy cases by reporting type



Pregnancy outcomes

- A summary of the pregnancy outcomes and exposure by trimester are presented in **Table 1**

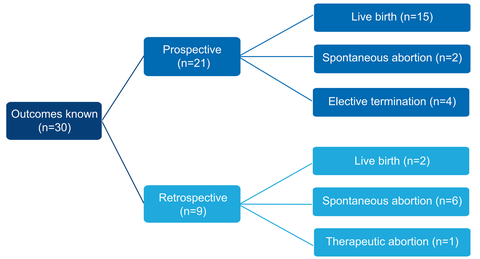
Table 1. Pregnancy outcome and exposure by trimester

			Prospective pregnancy			Retrospective pregnancy	
Pregnancy outcome	**Total cases**	**Peri-LMP***	**First trimester**	**Unknown trimester**	**Peri-LMP***	**First trimester**	**Unknown trimester**
Live birth	17	1	3	11	0	0	2
Spontaneous abortion	8	0	1	1	0	5	1
Therapeutic abortion	1	0	0	0	1	0	0
Elective termination	4	1	3	0	0	0	0
Ongoing pregnancy	13	0	11	2	0	0	0
Outcome not reported	18	0	9	9	0	0	0

*Peri-LMP period for ofatumumab: 180 days prior to LMP. LMP, last menstrual period.

- As of the cut-off date, outcomes were known in 30 pregnancies (**Figure 2**)
  - **Prospective pregnancies:** 15 live births, 2 spontaneous abortions and 4 elective terminations
    - Spontaneous abortion: one 33-year-old patient with hyperlipidemia, ectopic pregnancy and limited information is available in the second case
    - Reported reasons for elective termination were ectopic pregnancy (n=1), fear of potential fetal anomaly (n=1) and anembryonic pregnancy (n=1) and reason was not reported in one case

Figure 2. Pregnancy outcomes in women with RMS exposed to ofatumumab



  - **Retrospective pregnancies:** 2 live births, 6 spontaneous abortions and 1 therapeutic abortion
    - Spontaneous abortion (n=6):
      - A 29-year-old patient with history of ectopic pregnancy and chronic iron deficiency anemia
      - A 43-year-old patient, who reported the reason for abortion as advancing age
      - A 29-year-old patient reported with history of smoking and surgical abortion reported abortion at 5.5 weeks
      - A 36-year-old patient reported spontaneous abortion at 9 weeks due to stunted growth of fetus
      - In remaining 2 patients, information is limited
    - Therapeutic abortion: n=1, was reported retrospectively due to fetal death
- Although the number of prospective cases is currently low, the frequency of spontaneous abortions is comparable to that seen in general MS population (10.9%, 95%CI 5.2-18.3%) and MS patients treated with other DMTs (11.6%, 95%CI 7.4%-16.7%)[8]

Infant outcomes

- In the 17 live births, there were no congenital anomalies, or congenital malformations reported
  - In the 17 live births, there were no B-cell depletion, immunoglobulin/ hematological abnormalities, or serious infections that were voluntarily reported during follow-up period of 1 year

Conclusions

- A total of 61 pregnancies in women with RMS exposed to ofatumumab were reported, with 30 known outcomes (prospective pregnancies, 21; retrospective 9)
- No congenital anomalies, or congenital malformations were reported in the 17 live births
- Ofatumumab treatment should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus
- The data on pregnancy outcomes in pregnant women exposed to ofatumumab is limited. Novartis will continue to collect information on pregnancy outcomes from maternal cases exposed to ofatumumab, to assess the risk of reproductive toxicity in these patients
- A prospective observational registry on maternal and infant outcomes in women exposed to ofatumumab is currently being developed in US/Canada and Germany

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