Pregnancy Outcomes in Patients With Multiple Sclerosis Following Exposure to Ofatumumab

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Disclosures

Author Name	Disclosures
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Background & Objective

Background

- Ofatumumab FDA and EMA label states women of childbearing potential should use effective contraception during the treatment with ofatumumab and for 6 months after the last dose[1,2]
- In cynomolgus monkeys, exposure to ofatumumab during gestation did not cause maternal toxicity, and no adverse effects were observed on the prenatal or postnatal development[3]
- Data on the effect of ofatumumab on pregnancy outcomes are limited in humans. Based on the current knowledge
  - 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 born to mothers exposed to other anti-CD20 antibodies during pregnancy[1,5,6]
  - no congenital anomalies were previously reported in 13 pregnant women with chronic lymphocytic leukemia (CLL) when exposed to higher doses of ofatumumab[7]

Objective

- To report pregnancy and infant outcomes from the Novartis Safety Database in women inadvertently exposed to ofatumumab for the treatment of relapsing multiple sclerosis (RMS) or other indications

1. Kesimpta (ofatumumab). Prescribing Information. Accessed October 11, 2021. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf; 2. Kesimpta (ofatumumab). Summary of product characteristics. Accessed October 15, 2021. https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf; 3. Bellot M, et al. Poster presented at: AAN 2021; November 5-7, 2021; 4. Pentsuk N, van der Laan JW. *Birth Defects Res B Dev Reprod Toxicol*. 2009;86(4):328-344; 5. Chakravarty EF, et al. *Blood* 2011;117:1499–1506 ; 6. Das G, et al. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e453; 7. Data on file.

Methods

- Pregnancy outcomes data from women exposed to ofatumumab during or prior to pregnancy were analyzed
  - For ofatumumab, exposure within 6 months of the last menstrual period (LMP) to ofatumumab treatment is defined as maternal exposure during pregnancy
- Pregnancy and infant outcomes with a data cutoff of August 31, 2021 reported from clinical trials and post-marketing data to the Novartis Safety Database were collected

- 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[a]

- therapeutic/induced abortion
- spontaneous abortion
- intrauterine fetal demise (IUFD) includes still birth
- live birth

Infant outcomes

- birth defects
- congenital anomalies
- infections
- vaccination and
- developmental delays

[a]Therapeutic/induced abortion: Abortion due to abnormal fetus, fetal death, risk to the mother, or choice of mother of an otherwise normal fetus. Spontaneous abortion: The fetus is spontaneously aborted prior to 22 weeks' gestation; prior fetal status via prenatal testing may or may not be known. IUFD: Fetal demise confirmed by prenatal tests, followed by a spontaneous abortion or requiring a therapeutic abortion, or stillbirth (the patient gives birth to a still born, ie, no signs of life at or after 22 weeks of gestation is completed). Live birth: patient gives birth to a live neonate

Results: Pregnancy Outcomes

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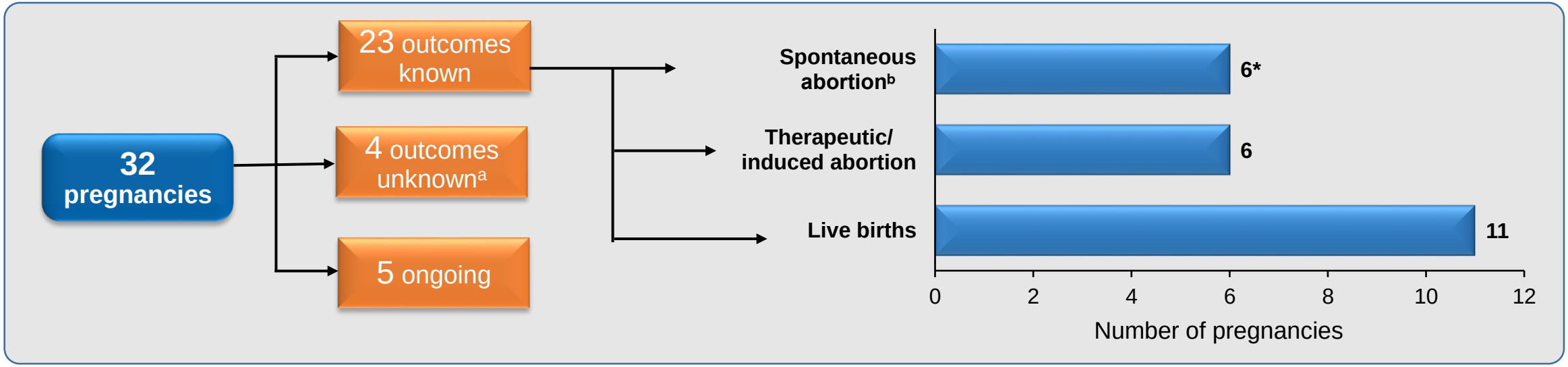
Pregnancy outcomes in women with RMS exposed to ofatumumab

- As of the cutoff date August 31, 2021, 32 pregnancies were reported in women with MS who were exposed to ofatumumab
  - ASCLEPIOS I/II, n=4; ALITHIOS, n=14; MIRROR, n=7; postmarketing, n=7
  - Exposure to ofatumumab treatment after LMP: n=12; within 6 months prior to LMP: n=4; timing unknown, n=16
  - Mean (range) age: 32 (20-43) years
- In addition, 1 pregnancy was reported (ASCLEPIOS I/II) with exposure to ofatumumab greater than 6 months prior to LMP



IUFD, intrauterine fetal demise; LMP, last menstrual period; MS, multiple sclerosis; RMS, relapsing multiple sclerosis.
*Includes one case which was previously labelled as early IUFD. Based on expert opinion, this case later reclassified as spontaneous abortion
[a]Queries are pending. [b]The rate of spontaneous abortion in normal individuals is 12%-24% (Facco F et al. Principles and Practice of Sleep Medicine (Sixth Edition) 2017;1540-1546.e4)

Results: Infant Outcomes and Other Results

Infant outcomes in women with RMS exposed to ofatumumab

- One case exposed to ofatumumab >6 months prior to LMP resulted in a live birth
- No reports of B-cell depletion, immunoglobulin/hematological/fetal abnormalities, and serious infections in infants followed up
  - Of the 11 live births as of cutoff date, 0, 1, 1 and 2 were followed up for 1 year, 9 month, 6 month and 1 month of follow-up, respectively, 1 case was lost to follow-up after 2 months, and 6 cases were not followed up
  - 9 infants have crossed 1 year of age and 2 infants are yet to reach 1 year of age

No congenital anomalies and no reports of B-cell depletion, immunoglobulin/hematological/fetal abnormalities, and no serious infections were reported in the babies

Pregnancy and infant outcomes in women with other indications reported in the Novartis database (cutoff: 8/31/21)

- Two pregnancies were reported (both from OFA110634 study) in women with rheumatoid arthritis and exposed to ofatumumab (700 mg X 2 intravenous infusions two weeks apart)
  - One resulted in a live birth
  - Another resulted in therapeutic/induced abortion

LMP, last menstrual period.

Conclusions

- From the Novartis safety database with the current data cutoff (August 31, 2021), a total of 32 pregnancies in women with RMS inadvertently exposed to ofatumumab were reported, with 23 known outcomes
  - 11 live births, 6 therapeutic/induced abortions, and 6 spontaneous abortions
  - No birth defects or congenital anomalies were reported in 11 pregnant women who had live births
- Based on the data from follow-up on the 11 live births,
  - There were no reports of B-cell depletion, immunoglobulin/hematological abnormalities, or serious infections specified
- From the limited data in other indications from this database, there were no birth defects or congenital anomalies reported
- Ofatumumab treatment should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus
- Early treatment interruption upon unplanned/expected pregnancy could pose low risk of fetal exposure owing to ofatumumab's short half-life (t1/2) of approx. 16 days and average clearance within 12 weeks (5 times of t1/2)
- Sharing the latest data on pregnancy and infant outcomes with ofatumumab use could be helpful in counseling women with MS of childbearing potential
- A prospective observational registry on maternal and infant outcomes in women exposed to ofatumumab is currently underway

MS, multiple sclerosis; RMS, relapsing multiple sclerosis; t1/2, half-life.