1 ABSTRACT

Title

International LEMTRADA Pregnancy Exposure Cohort in Multiple Sclerosis

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Keywords

Pregnancy, registry, multiple sclerosis, alemtuzumab, safety

Rationale and background

LEMTRADA® is a recombinant humanized monoclonal antibody for intravenous infusion indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). LEMTRADA binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. The mechanism by which LEMTRADA exerts its therapeutic effects in MS is unknown but may involve immunomodulation through the depletion and repopulation of lymphocytes.

At the time of protocol development, there were no adequate and well-controlled studies of LEMTRADA in pregnant women. It was not known whether LEMTRADA could affect reproductive capacity or cause fetal harm when administered to a pregnant woman.

Research question and study objectives

This post authorization safety study (PASS) was an international, observational cohort study (registry) of pregnancy outcomes in women with MS exposed to LEMTRADA during pregnancy.

The overall goal of this registry was to compare maternal, fetal, and infant outcomes in women exposed to LEMTRADA with the outcomes in women from unexposed external comparison groups during pregnancy and to assess if the risks of any adverse pregnancy outcomes and birth defects in women exposed to LEMTRADA during pregnancy exceeded the risks in women of unexposed external comparison groups. However, these comparisons were not performed because the number of patients recruited was lower than planned and the study was stopped early.

This registry planned to detect and record the following outcomes:

- Primary outcome:
  - Spontaneous abortion
- Secondary outcomes:
  - Major and minor congenital malformations

- Pregnancy outcome: stillbirth, elective terminations, preterm live birth, full-term live birth
- Small for gestational age at birth
- Any other adverse pregnancy outcomes

These outcomes were assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, were assessed through the first year of life.

Study design

This was an observational study with no experimental intervention utilized. Women enrolled in the study received treatment and evaluations for their MS and their pregnancies as determined by their treating physicians in accordance with local standard of care. Information of prospective pregnancies on patient's safety and pregnancy outcome was collected during each trimester and within 6 weeks after the end of pregnancy. For all live births, the infant's Health Care Provider (HCP) was contacted at 1-year postdelivery to obtain follow-up on the infant's health status. Information of retrospective pregnancies (exposed to LEMTRADA during pregnancy but pregnancy outcome was known at time of registry) was to be collected similarly, except for information on the chronological interview during pregnancy (ie, the information collected via interview during each trimester and at the pregnancy outcome interview within 6 weeks after the end of the pregnancy).

The total duration of the study was expected to be approximately 5 years.

Setting

- Site and participant selection: Women with MS who were or became pregnant within the period of time between the first infusion of a course of treatment with LEMTRADA to 4 months after their last infusion for that course, and were able and willing to provide informed consent, were eligible to participate. Women exposed to LEMTRADA during pregnancy were recruited from a variety of sources, including referral of female patients who became pregnant while enrolled in a separate observational study; referral of LEMTRADA-exposed female patients reporting pregnancies identified through routine pharmacovigilance activities, and LEMTRADA-exposed female patients reporting pregnancies identified through study outreach activities such as study postings on applicable websites. An open enrollment approach was used to maximize enrollment. Any eligible woman receiving health care in a country in which this study was operating was encouraged to participate through her HCP(s) and the National Coordinator. There was no forced selection process for patients or physician reporters in this protocol; therefore, prospectively enrolled women were expected to be representative of the source population in the respective countries.
- Overall participation status: This registry planned to enroll pregnant women with MS who had any pregnancy exposure to LEMTRADA between 10 August 2015 and 22 November 2021 from North America, Europe, and the rest of the world.

- Data collection: Forms with patients' data completed by the HCP were sent to the National Coordinator who entered the data into the electronic case report form (eCRF). Birth defect evaluation forms were completed by the Birth Defect Evaluator (BDE) and data were entered into the eCRF by the Marketing Authorization Holder (MAH)/MAH representative. The MAH/MAH representative completed the Targeted Follow-up Forms for birth defects and entered data into the eCRF.

Participants and study size, including dropouts

A total of approximately 204 women exposed to LEMTRADA during pregnancy (prospective) were planned to be enrolled to achieve approximately 193 women followed up to 1 year postdelivery, allowing approximately 5% of recruited women to have missing pregnancy outcome data.

Variables and data sources

- **Data management, review, validation:** Data were entered into a study-specific database and maintained by the National Coordinator. All data entry was reviewed for logical errors by the National Coordinator. Subsequent review of data was performed by the MAH/MAH representative and 100% of key variables were double-checked for accuracy of data entry. The study statistician of the MAH/MAH representative also conducted reviews of the cumulative data from the study database.
- **Statistical considerations:**

  This PASS report summarizes the maternal, fetal, and infant outcomes (including birth defects) in women with MS exposed to LEMTRADA during pregnancy.

  Data analyses were performed according to the following general considerations: Descriptive statistics for continuous/quantitative data included the number of patients with nonmissing data (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics for categorical/qualitative data included the number of nonmissing data, counts, and percentages. Confidence intervals (CIs) were reported as 2-sided. Missing data or unknown responses were not counted in the percentages. Missing data were not imputed except for missing dates of last menstrual period (LMP) and missing or partial adverse event (AE) onset dates and times.
- **Variables and evaluation criteria:** The primary variable in this registry was spontaneous abortion (<20 gestation weeks). Other variables included pregnancy and fetal outcomes (ie, full-term live birth, preterm live birth, fetal death [ie, stillbirth, ≥20 gestation weeks], Termination of Pregnancy for Fetal Abnormality (TOPFA), induced abortion [ie, elective termination without evidence of birth defects], ectopic pregnancy, molar pregnancy, and any other pregnancy outcomes), small for gestational age at birth, birth defects (classified as major or minor congenital malformations), pregnancy exposure to LEMTRADA, and AEs.
- **Data analyses:**

  For the main evaluation variable (ie, a woman's pregnancy outcome of spontaneous abortion [<20 weeks gestation in all the fetuses of the pregnancy]), the number and rate of

spontaneous abortions were presented. The number and rate of each of the secondary evaluation variables (ie, major and minor congenital malformations [birth defects], pregnancy outcomes, and infants small for gestational age at birth) were presented. The birth defect rate was calculated based on European Surveillance of Congenital Anomalies (EUROCAT) and the Center for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (MACDP) conventions. Other variables were presented using descriptive statistics.

It should be noted that the term "rate" has been used, although the point estimates calculated actually represent the "risk." In studies with short-term follow-up such as this registry, the rate and risk are similar, and the term "rate" is commonly used.

Results

- **Overall participation status:**

  The country of residence for the majority of women in the Enrolled Women Population was Germany (20 women [44.4%]). This was followed by Spain (5 women [11.1%]); Canada, Great Britain, and Italy (3 women [6.7%] each); Austria, Belgium, Sweden, and United States (2 women [4.4%] each); and Australia, Denmark, and the Netherlands (1 woman [2.2%] each).

- **Participation per period of the study:**

  In total, 45 women were included in the Enrolled Women Population (ie, all women who were enrolled in the registry regardless of whether they met the inclusion criteria/exclusion criteria). All 45 women in the Enrolled Women Population were prospective cases; there were no retrospective cases.

  The Evaluable Women Population included 42 women who met the inclusion/exclusion criteria and had a recorded pregnancy outcome.

  The Enrolled but not Evaluable Women Population included 3 women who did not meet the inclusion/exclusion criteria or did not have a recorded pregnancy outcome. None of the 3 women in the Enrolled but not Evaluable Population took LEMTRADA during pregnancy so they did not meet the inclusion criteria and 2 of these women had no recorded pregnancy outcome.

  There were 43 infants/fetuses in the All Infants/Fetuses Population (ie, all infants or fetuses [regardless of pregnancy outcome] from the 42 women in the Evaluable Women Population). This included 1 set of twins and 1 spontaneous abortion.

  There were 43 infants in the Live Born Infants Population (ie, all live-born infants from the 45 women in the Enrolled Women Population). This included 1 infant from a woman who was included in the Enrolled Women Population but was excluded from the Evaluable Women Population because she did not meet the inclusion criteria (ie, she did not take LEMTRADA during pregnancy) and 1 set of twins.

  Of the 43 infants in the Live Born Infants Population, 36 infants were alive at the 1-year follow-up assessment, 2 infants were dead, 3 infants were lost to follow-up, and 2 infants

were not yet due the 1-year follow-up assessment because the study was discontinued early.

- **Descriptive data:**

  Demographics and baseline characteristics

  All 45 women (100%) in the Enrolled Women Population had relapsing-remitting MS; the mean time from diagnosis to enrollment was 7.5 years (SD 4.85 years). The mean age at conception was 29.7 years (SD 4.37 years) and the mean gestational age at enrollment was 17.2 weeks (SD 14.28 weeks). Tobacco use was reported prior to conception in 16 women (35.6%), during the first trimester in 7 women (15.6%), and during the second and third trimesters in 1 woman (2.2%). Eleven women (24.4%) reported alcohol use prior to conception, and 2 women (4.4%) reported alcohol use during the first trimester. One woman (2.3%) reported a history of substance abuse. Four women (9.5%) had previously had a spontaneous abortion, and 4 women (9.5%) had previously had an elective termination with no or unknown fetal defects. There were no previous live births with abnormalities and no previous elective terminations with fetal defects. Of the 44 women who had data on exposure to LEMTRADA, the earliest exposure was prior to conception in 33 women (75.0%) and less than 13 weeks of gestation in 11 women (25.0%).

  Exposure to LEMTRADA

  The recommended dosage of LEMTRADA is a first treatment course of 12 mg/day on 5 consecutive days and a second treatment course of 12 mg/day on 3 consecutive days administered 12 months after the first treatment course. Up to 2 additional treatment courses, as needed, may be considered (12 mg/day on 3 consecutive days administered at least 12 months after the prior treatment course). The mean duration of LEMTRADA intake in women in the Evaluable Women Population during pregnancy was 1.1 days (SD 1.96 days) and the mean duration of LEMTRADA intake before conception was 4.8 days (SD 2.94 days). The mean duration of LEMTRADA exposure to the fetus was 9.09 weeks (SD 6.77 weeks).

  Infant demographics and baseline characteristics

  Of the 43 infants in the Live Born Infants Population, 30 infants (69.8%) were male, and 13 infants (30.2%) were female. Delivery was vaginal for 36 infants (85.7%) and by Caesarean section for 6 infants (14.3%); delivery mode was not reported for 1 infant. At 1 minute, Apgar scores were recorded for 32/43 infants in the Live Born Infants Population; median recorded Apgar score was 9.0 (range 2 to 10). At 5 minutes, Apgar scores were recorded for 38/43 infants in the Live Born Infants Population; median recorded Apgar score was 10.0 (range 1 to 10). Median week of gestation at birth was 39.0 weeks (range 22 to 41 weeks; mean 38.4 weeks [SD 3.99 weeks]). Mean birth weight was 3138 g (SD 733 g); birth weight ranged from 490 g to 4290 g. Thirty-six infants (90.0%) were an appropriate size relative to their gestational age, 2 infants (5.0%) were small for gestational age, 2 infants (5.0%) were large for gestational age, and relative size data were not available for 3 infants.

Pregnancy outcomes

Thirty-eight women (90.5%) in the Evaluable Women Population had a full-term live birth (≥37 weeks; 38 children), 3 women (7.1%) had a preterm live infant (<37 weeks; 4 children [including 1 set of twins]), and 1 woman (2.4%) had a spontaneous abortion (<20 gestation weeks; 1 fetus). There were no cases of fetal death (≥20 gestation weeks [ie, stillbirth]), ectopic pregnancy, molar pregnancy, TOPFA, or induced abortion (ie, elective termination without evidence of birth defects). There were no other adverse pregnancy outcomes.

The point estimate for the rate of spontaneous abortion (ie, the number of pregnancies with a spontaneous abortion divided by the number of evaluable prospective women who were exposed to LEMTRADA before 20 weeks of gestation) was 0.02 (95% CI: 0.00, 0.13).

Major and minor congenital malformations

Overall, in the All Infants/Fetuses Population, there were 2 infants with major congenital malformations and 2 infants with minor congenital malformations. Per EUROCAT coding, 2 patients (4.8%) in the Evaluable Women Population had an infant with at least 1 birth defect. These were both major defects (1 defect in each infant); there were no minor defects per EUROCAT coding. Per MACDP coding, 4 patients (9.5%) in the Evaluable Women Population had an infant with at least 1 birth defect; 2 infants had 1 major birth defect each, and 2 infants had 1 minor birth defect each.

Small for gestational age at birth

Two women in the Evaluable Women Population restricted to women without multiples had an infant that was small for gestational age at birth. The point estimate for the rate of small for gestational age at birth was 0.05 (95% CI: 0.00, 0.17).

Infant characteristics at the 1-year follow-up assessment

Of the 43 infants in the Live Born Infants Population, 36 infants were alive at the 1-year follow-up assessment (including the infants with birth defects), 2 infants were dead, 3 infants were lost to follow-up, and 2 infants were not yet due the 1-year follow-up assessment because the study was discontinued early. The median age at the 1-year follow-up was 12.0 months, ranging from 11 to 20 months (n = 36). Mean weight was 9.90 kg (SD 1.17 kg), ranging from 8.1 kg to 14.0 kg (n = 32). At the 1-year follow-up, 29 infants (90.6%) were an appropriate size relative to their age and 3 infants (9.4%) were large relative to their age (n = 32). The mean weight-for-age z-score (measured weight – average weight in the World Health Organization [WHO] reference population)/SD of the WHO reference population) was 0.28 (SD 0.97), ranging from -1.59 to 3.48 (n = 32). There were no new birth defects or other infant conditions recorded at the 1-year follow-up. None of the 36 infants with data recorded at the 1-year follow-up had areas of developmental concern or functional deficit.

Adverse events in women

In total, 19 women (42.2%) in the Enrolled Women Population had at least 1 treatment-emergent AE (TEAE); in 3 of these women (6.7%) the TEAE was considered related to LEMTRADA (hypothyroidism [2 women] and hyperthyroidism [1 woman]).

Four women (8.9%) had a serious TEAE, including a serious TEAE of foetal heart rate abnormal (reported term: uterine dilatation and curettage [no infant-heartbeat]) in the woman who had a spontaneous abortion. None of the serious TEAEs in women were considered related to LEMTRADA and there were no TEAEs that resulted in death.

Adverse events in infants/fetuses

In total, 23 infants (53.5%) in the Live Born Infants Population had at least 1 AE. None of the AEs in the Live Born Infants Population were considered related to LEMTRADA. Fourteen infants (32.6%) in the Live Born Infants Population had a serious AE (SAE), and 2 infants (4.7%) had an AE that resulted in death.

One fetus (spontaneous abortion) who was excluded from the Live Born Infants Population had an SAE of cardiac arrest, which resulted in death, and was considered related to LEMTRADA. On the same date, the mother had a serious TEAE of foetal heart rate abnormal (reported term: uterine dilatation and curettage [no infant-heartbeat]).

Discussion

This report reflects the results from a registry for an infrequent condition (pregnancy exposed to LEMTRADA). The planned comparisons of outcomes from this registry with those from external comparison groups unexposed to LEMTRADA could not be performed because of the low number of patients recruited.

The main evaluation variable was the rate of spontaneous abortion. One of 42 women (2.4%) in the Evaluable Women Population had a spontaneous abortion. The death of this fetus (fatal SAE of cardiac arrest) was considered related to LEMTRADA. The other pregnancy outcomes included 38 women (90.5%) who had a full-term live birth (≥37 weeks), and 3 women (7.1%) who had a preterm live infant (<37 weeks). There were no cases of fetal death (≥20 gestation weeks [ie, stillbirth]), ectopic pregnancy, molar pregnancy, TOPFA, or induced abortion (ie, elective termination without evidence of birth defects). There were no other adverse pregnancy outcomes.

Two infants had major congenital malformations (birth defects) at birth according to EUROCAT and MACDP conventions and 2 infants had minor congenital malformations at birth according to MACDP conventions. None of the birth defects were considered related to LEMTRADA. There were no new birth defects or other infant conditions recorded at the 1-year follow-up. None of the 36 infants with data recorded at the 1-year follow-up had areas of developmental concern or functional deficit.

The incidence of spontaneous abortion in this registry was lower than observed in previous studies in alemtuzumab-treated patients with relapsing-remitting MS (2.4% in the current registry versus 22% in previous studies) but the low number of patients in this registry should be taken into consideration. The spontaneous abortion (fatal SAE of cardiac arrest) was considered related to LEMTRADA.

Marketing Authorization Holder

The MAH is Genzyme Corporation in the United States and Sanofi Belgium in the European Union.

Marketing Authorization Holder's Representative

The MAH representative for this registry is Syneos Health® (previously INC Research LLC), a contract research organization (CRO) delegated to serve as the Study (Registry) Coordinating Center for this registry, responsible for the operational conduct of the registry including recruiting, training, and remote monitoring of the National Coordinators throughout the duration of the registry, facilitating data collection through the National Coordinators, ensuring adherence to local regulations including data privacy, overseeing the work of the National Coordinators, performing the data management and statistical analyses, and drafting the study report and other study documents.

Study Personnel

The Scientific Advisory Committee (SAC) Chairperson's and Company's responsible medical officer's signed approvals of the report are provided in Annex 2.

This report was prepared by [redacted]

The report was reviewed by:

[redacted]

The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

Names and affiliations of Principal Investigators

Not applicable.

National Coordinators

See List of National Coordinators.