2. ABSTRACT

Title

Belimumab (BENLYSTA) Pregnancy Registry (BEL114256) Final Analysis Report

Keywords

Belimumab, pregnancy exposure registry, pregnancy outcomes, birth defects

Rationale and background

Systemic lupus erythematosus (SLE) is a disabling and life-threatening chronic autoimmune condition that can impact any organ system. To date, there is no cure for SLE, and people with SLE may experience a heavy clinical burden of poor or untimely diagnosis, use of multiple toxic medications, and significant impacts on quality of life and activities of daily living.

Belimumab is a recombinant, human, immunoglobulin G1λ monoclonal antibody that binds soluble B lymphocyte stimulator (BLyS) with high affinity and inhibits its biological activity. Following in vitro and animal model studies, belimumab was identified as a potential therapeutic agent for autoimmune diseases in which BLyS may play a role in disease pathogenesis. Belimumab was the first biologic agent approved for the treatment of SLE; however, data from human subjects who received substantial exposure to belimumab during pregnancy are lacking.

Research questions and objectives

The purpose of the Belimumab Pregnancy Registry (BPR) was to evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to commercially supplied belimumab within the four months' preconception and/or during pregnancy and outcomes for pregnancies in women with SLE who were not exposed to belimumab and were enrolled through the Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus (SABLE) registry. The primary endpoint was birth defect, defined as any major structural or chromosomal defect or combination of two or more conditional defects in live-born infants, stillbirths, or fetal losses (spontaneous miscarriage, stillbirth, ectopic pregnancy, and molar pregnancy) of any gestational age (including outcomes prior to $20^{0/7}$ weeks' gestational age or weighing <500 g). This definition was consistent with, but not restricted to, the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) definition. Secondary endpoints included spontaneous miscarriage, live birth (including full-term birth, preterm birth, small-for-gestational-age [SGA], neonatal death), elective termination, stillbirth, and serious infections and/or non-serious infection/fevers (clinically significant as per protocol) and developmental milestones met in infants through one year of age.

The overall goal of the BPR was to collect data on real-word reproductive experience with belimumab to complement reproductive data from animal toxicology studies.

Study design

The BPR was a global, prospective cohort study with voluntary participant registration following informed consent by the pregnant woman for her participation and assent for participation of her infant. Between 16 July 2012 and 28 October 2022, the BPR recruited and enrolled women with SLE exposed to commercially supplied belimumab within the four months' preconception and/or during pregnancy; the protocol planned to collect outcome information for pregnancies in women with SLE who were not exposed to belimumab while participating in the SABLE protocol and enrolled in the BPR. Data were collected at the time of enrollment, at the end of the second trimester (at approximately 26 weeks' gestation), and at pregnancy outcome. For pregnancies that resulted in live births, infant outcomes at the time of birth were reported. Infant follow-up information was collected at 4 and 12 months of age. Retrospective reports of pregnancy were those in which the pregnancy outcome occurred before enrollment into the BPR or at the time of first contact with the BPR. Data collected for the retrospective cases were entered into the electronic data capturing (EDC) system using the same procedure as the prospective cases but were summarized separately.

Setting

The registry was strictly observational; the schedule of office visits and all treatment regimens was determined by the treating healthcare provider (HCP). The registry collected data that were routinely documented in the participant's medical record during usual clinical care.

Participants and study size

A total of 87 pregnant individuals with SLE who were exposed to commercially supplied belimumab within four months' preconception and/or during pregnancy consented and enrolled into the BPR. Of the 87 pregnant individuals, two had previously enrolled in a belimumab clinical trial and five previously enrolled in the BPR. Among the 87 pregnant individuals, 72 (82.8%) were considered evaluable with confirmed outcomes and 15 were considered unevaluable, which included 10 participants who were deemed invalid or ineligible, five participants who were considered lost-to-follow-up prior to pregnancy outcome, and none with unconfirmed pregnancy or exposure. Among the 72 evaluable pregnant individuals with confirmed pregnancy outcomes, 61 (84.7%) individuals were pregnant at the time of enrollment and were prospectively enrolled into the main study cohort to assess the key outcomes of the study. The remaining 11 (15.3%) of 72 individuals were included as retrospective reports as they had completed pregnancies (such as live birth or spontaneous miscarriage) prior to enrollment and were summarized separately) No unexposed pregnant individuals with SLE from SABLE enrolled into the BPR.

Variables and data sources

Registry enrollment was voluntary and could be initiated by pregnant women or their HCPs, who acted as data reporters to the registry. After informed consent was obtained from eligible women, the participant and/or her HCPs completed the ***Registration Form*** and the initial HCP data collection forms and submit them to the registry.

Following registry enrollment of participants, confirmation of commercially supplied belimumab exposure was obtained from the HCP (primarily from the belimumab prescriber or the infusion center, but confirmation was accepted from alternate HCPs). Confirmation of pregnancy was obtained from any HCP. Data were collected at three timepoints: at enrollment (maternal demographics, exposure information, disease severity, medical and pregnancy history, concurrent medical conditions, concomitant medications, and maternal adverse events [AEs]); at the end of the second trimester of pregnancy (approximately 26 weeks' gestational age) for which data collected at enrollment were updated and pregnancy/outcome status was assessed; and at pregnancy outcome (outcome of the pregnancy, characteristics of live-born infants, birth defects, and maternal AEs). For live births, infant data (anthropometrics, infections, developmental milestones, birth defects, and AEs) were collected at pregnancy outcome, at 4 months of age, and at 12 months of age. A hierarchy for source data was established to maximize the collection of key data points. For example, data on SLE disease severity were sought from the belimumab prescriber or other HCP; data regarding the pregnancy and pregnancy outcome were sought primarily from the obstetric HCP and secondarily from alternate HCPs (SLE prescriber or pediatric HCP), and data on live-born infants were sought primarily from the pediatric HCP and alternatively from the obstetrical (OB) HCP or SLE prescriber.

Results

Between 16 July 2012 and 28 October 2022, a total of 61 evaluable pregnant individuals with confirmed pregnancy outcomes in the prospective cohort were enrolled in the BPR of which half (n=32, 52%) were enrolled in the first trimester of pregnancy and 44 (72.1%) had prenatal testing prior to enrollment. The majority (n=49, 80.3%) of the prospective cohort were participants from the US, nearly three-quarters (n=45, 73.8%) were White or Caucasian and the mean maternal age (SD) was 31.9 (4.60) years.

Among the 61 pregnant individuals in the prospective cohort, the earliest period of exposure to belimumab was within the four months' preconception for almost all individuals (n=57, 93.4%). For four individuals, the earliest period of exposure to belimumab was the first (n=2) or the second (n=2) trimester. Last belimumab exposure occurred in the first trimester for nine (14.8%) individuals, in the second trimester for 32 (52.5%) individuals, in the third trimester for one (1.6%) individual, and in the post-pregnancy period for 19 (31.1%) individuals.

There were 61 pregnancies, of which one was a stillbirth and three were spontaneous miscarriages (one twin pregnancy resulted in one spontaneous miscarriage and one live birth). Of the 58 pregnancies with a live birth, there were 61 live birth infants (54 singleton pregnancies and seven live birth infants from four twin pregnancies).

Of the 61 live birth infants, 42 (68.9%) were full-term and 19 (31.1%) were preterm. Among the 54 singleton pregnancies that resulted in live birth infants, 14 (25.9%) were preterm (defined as infant born at $<37^{0/7}$ weeks); in addition, five of seven live birth infants (71.4%) from twin pregnancies were preterm infants.

Among the 61 live birth pregnancies in the prospective cohort enrolled prior to 20 weeks' gestation, four live birth pregnancies resulted in infants that were considered as SGA

based on the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) standards (6.6%; 95% confidence interval [CI]: 0.3% – 12.8%), and 12 live birth pregnancies resulted in infants that were considered SGA based on Alexander criteria (19.7%; 95% CI: 9.7% – 29.6%).

Among the 61 live birth infants from 58 prospective live birth pregnancies, 11 resulted in a major birth defect (using MACDP definition) as confirmed by the BDE (birth defect evaluator) (11/61, 18.0%; 95% CI: 8.4% – 27.7 %) while 12 resulted in a major birth defection when using either MADCP or European Surveillance of Congenital Anomalies (EUROCAT) (12/61, 19.7%; 95% CI: 9.7% to 29.6%). There was no indication or pattern of birth defects associated with belimumab.

There were 17 defect events among the 12 infants (five infants had two defects), using either/or MACDP/ EUROCAT. Five infants had defect events considered to be defects of known cause or no temporal association, and two infants had defect events with insufficient data on defect and/or belimumab exposure window for proper assessment.

Of the 12 live birth pregnancies with major birth defects, the earliest belimumab exposure occurred pre-conceptionally in 11 (91.7%) individuals and the mean (SD) cumulative belimumab exposure was 223.3 (79.03) days. Eleven (91.7%) had prenatal testing prior to enrollment of which one had an abnormal result (infant with atrial septal defect) and one where results were not available (Arnold Chiari type II malformation). Six (50.0%) were of advanced maternal age (35 to 39 years), one (8.3%) with a multiple gestation, and one (8.3%) reported an elective termination in a previous pregnancy.

Seven (58.3%) of the 12 live birth pregnancies with major birth defects had the presence of one or more comorbidity and/or pregnancy complication. Five (41.7%) infants from the 12 live birth pregnancies with a preterm birth and two were SGA. Exposure to concomitant medications of interest during pregnancy in the 12 live birth pregnancies included antimalarials (n=10, 83.3%), corticosteroids (n=6, 50.0%), aspirin (n=4, 33.3%), azathioprine (n=2, 16.7%), heparin (n=2, 16.7%), antiepileptics (n=2, 16.7%), cyclosporin (n=1, 8.3%); exposure of these drugs occurred in all three trimesters. Other concomitant medication exposure during pregnancy included NSAIDs (n=2, 16.7%); one across all trimesters, and one in the third trimester) and methotrexate (n=1, 8.3%, at first trimester).

Of the overall 61 live birth infants in the prospective cohort, four (6.6%) reported a serious infection during the first year of life (five events); 2 infants at outcome visit and 2 at 12-month visit. Fourteen (23.0%) of the 61 live birth infants reported non-serious infection/fevers (clinically significant per protocol definition) with a total of 16 events; two infants were identified at outcome visit, 7 infants at 4 month, and 6 infants at 12 months.

In total, 28 maternal serious adverse events (SAEs) were reported in 19 (31.1%) pregnant individuals in the prospective cohort and 18 (29.5%) pregnant individuals reported at least one maternal non-serious AE. In infants, 46 SAEs were reported in 26 pregnant individuals and there were 21 reports of individuals whose infants experienced at least one solicited non-serious AE.

A total of 11 retrospective pregnancies were enrolled within the BPR of which no confirmed major birth defects were identified in live birth infants as well no serious infections and/or non-serious infection/fevers (clinically significant per protocol) during infant one year follow-up. Pregnancy loss, excluding elective termination, occurred in 40% (4/10) pregnancies. These results should be interpreted with caution as the retrospective reports would be subject to biases since pregnancy outcome was known prior to enrollment.

Discussion

Of the sample size of 500 prospective pregnancies with a known outcome, only 61 (12%) were enrolled and considered evaluable for the study. Despite multiple awareness efforts to enroll patients into the BPR, enrollment targets were not achieved, and the registry was terminated early due to insufficient sample size. Based on the yearly enrollment rate (average of seven participants per year), the study as it was designed would need to be extended for 20 or more years to meet the targeted sample size. Coupled with the lack of an internal comparison group design, the BPR could not provide timely or clinically meaningful information to HCPs and patients.

Considering the limitations associated with the BPR, it was not possible to draw conclusions about any relationship between belimumab exposure and major birth defects using these data alone. However, the BPR did not identify any pattern of defects that would suggest an unusual cluster or plausible drug-induced mechanism of birth defects in individuals receiving belimumab within the data reported here or when observed in the wider context of limited case reports. The prevalence of other pregnancy and infant outcomes of interest align with published rates of these outcomes in pregnant women with SLE; however, due to the low number of outcomes accumulated in BPR to date, data should be interpreted with caution.

Conclusions

On 18 April 2023, the Belimumab Scientific Advisory Committee independently reviewed all data reported to the BPR as well as supplemental data and concluded that there are insufficient pregnancy outcomes to ascertain the risks of birth defects and the secondary endpoints of intent for pregnancy exposed to commercially supplied belimumab.

Marketing authorization holder

GSK (Ireland) Limited.