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Belimumab use during pregnancy: a summary of birth defects and pregnancy loss from belimumab clinical trials, a pregnancy registry and postmarketing reports

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ABSTRACT

Objective Describe available data on birth defects and pregnancy loss in women with systemic lupus erythematosus (SLE) exposed to belimumab.

Methods Data collected from belimumab clinical trials, the Belimumab Pregnancy Registry (BPR), and postmarketing/spontaneous reports up to 8 March 2020 were described. Belimumab exposure timing, concomitant medications and potential confounding factors were summarised descriptively.

Results Among 319 pregnancies with known outcomes (excluding elective terminations), 223 ended in live births from which birth defects were identified in 4/72 (5.6%) in belimumab-exposed pregnancies and 0/9 placebo-exposed pregnancies across 18 clinical trials, 10/46 (21.7%) belimumab-exposed pregnancies in the BPR prospective cohort (enrolled prior to pregnancy outcome) and 0/4 belimumab-exposed pregnancies in the BPR retrospective cohort (enrolled after pregnancy outcome), and 1/92 (1.1%) in belimumab-exposed pregnancies from postmarketing/spontaneous reports. There was no consistent pattern of birth defects across datasets. Out of pregnancies with known outcomes (excluding elective terminations), pregnancy loss occurred in 31.8% (35/110) of belimumab-exposed women and 43.8% (7/16) of placebo-exposed women in clinical trials; 4.2% (2/48) of women in the BPR prospective cohort and 50% (4/8) in the BPR retrospective cohort; and 31.4% (43/137) of belimumab-exposed women from postmarketing/spontaneous reports. All belimumab-exposed women in clinical trials and the BPR received concomitant medications and had confounding factors and/or missing data.

Conclusions Observations reported here add to limited data published on pregnancy outcomes following belimumab exposure. Low numbers of exposed pregnancies, presence of confounding factors/other biases, and incomplete information preclude informed recommendations regarding risk of birth defects and pregnancy loss with belimumab use.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Children of women with systemic lupus erythematosus (SLE) have a higher risk of birth defects than those born to women without SLE, and women with SLE are at increased risk of pregnancy loss. This is due to disease activity, antiphospholipid antibodies and exposure to certain commonly used SLE therapeutic agents. Belimumab is a targeted human IgG1 monoclonal antibody approved in patients ≥5 years of age for the treatment of active, autoantibody-positive SLE in combination with standard therapy.

⇒ Pregnant women are traditionally excluded from enrolling in clinical trials, and as such, there are limited safety data on the use of belimumab in pregnancy and any associated risk of birth defects and pregnancy loss.

WHAT THIS STUDY ADDS

⇒ This is the largest descriptive summary of birth defects and pregnancy losses among women exposed to belimumab during pregnancy. Data sources included belimumab clinical trials, the Belimumab Pregnancy Registry (BPR) and postmarketing/spontaneous reports of belimumab-exposed pregnant women with SLE.

⇒ Overall, among pregnancies ending in live birth, the numbers of birth defects in belimumab-exposed pregnancies were 4/72 (5.6%) in clinical trials, 10/46 (21.7%, ad hoc 95% CI 9.8% to 33.7%) and 0/4 in the BPR prospective and retrospective cohorts, respectively, and 1/92 (1.1%) in the postmarketing/spontaneous reports, with no consistent pattern of malformations. The numbers of pregnancy losses (out of pregnancies with known outcomes excluding elective terminations) were 35/110 (31.8%) in clinical trials, 2/48 (4.2%, ad hoc 95% CI 0.0 to 9.8%) and 4/8 (50.0%) in the BPR prospective and retrospective cohorts, respectively, and 43/137 (31.4%) in the postmarketing/spontaneous reports.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women of childbearing age and poses considerable risks to

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings add to the limited data available on outcomes following maternal exposure to belimumab during pregnancy. Due to small sample sizes, presence of confounding factors, limitations related to capture of complete information, heterogeneity of the data sources, and the fact that the clinical trials and postmarketing/spontaneous reports were not designed to assess pregnancy outcomes, they cannot be used to make informed recommendations regarding risk of birth defects and pregnancy loss following belimumab exposure. This highlights the need for an alternative approach related to future efforts to evaluate outcomes in women exposed to belimumab during pregnancy.

both mother and foetus during pregnancy.[1 2] SLE-related factors such as renal disease and presence of antiphospholipid antibodies have been associated with poor pregnancy outcomes, including pre-eclampsia/eclampsia, miscarriage, abortion, preterm birth and maternal death, compared with women without SLE.[3]

Children of women with SLE have a higher risk of birth defects than those born to women without SLE.[4–8] For instance, congenital heart block—a severe manifestation of neonatal lupus—has been associated with presence of the maternal autoantibodies anti-Ro/Sjögren's syndrome-related antigen A (SSA) and anti-La/Sjögren's syndrome-related antigen B (SSB), which can occur in SLE.[8–10] Analysis of data from the 2000–2011 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project found a 4% increased risk of miscarriage among women with SLE compared with pregnancies in women without SLE.[3] A meta-analysis of studies published between 2017 and 2019 that included 9696 SLE-associated pregnancies reported a significantly increased risk of stillbirth and pregnancy loss in pregnant women with SLE compared with those without SLE.[11]

Standard SLE therapeutic agents, such as cyclophosphamide, methotrexate and mycophenolate mofetil (MMF), have been implicated in birth defects and pregnancy loss.[1 12 13] A recent study suggested that there may be a small increased risk of birth defects after hydroxychloroquine exposure, although this finding is not consistent with other studies.[14–17] Medical organisations in Europe (European Alliance of Associations for Rheumatology) and in the USA (American College of Obstetrics and Gynecology and American College of Rheumatology (ACR)) recommend against the use of several high-risk agents including cyclophosphamide, MMF, mycophenolic acid, leflunomide and methotrexate during conception and pregnancy.[18–20] There are also limited birth defect data for novel SLE treatments, such as biologic drugs.[1] Therefore, SLE management often needs to be adjusted when pregnancy is planned, or when unplanned pregnancy is confirmed, to control disease while minimising harm.[1 20]

Belimumab is a disease-modifying biologic therapy that inhibits soluble B-lymphocyte stimulator (also known as B-cell activating factor),[21 22] with a distribution and terminal half-life of 1.8 and 19.4 days, respectively.[23] Efficacy and safety of belimumab plus standard therapy (ST) versus ST alone in patients with SLE have been demonstrated consistently across four phase III clinical trials.[24–27] Belimumab is indicated for treatment of active, autoantibody-positive SLE in patients aged 5 years and older who are undergoing ST. Belimumab was first approved in 2011 and is now approved in a number of regions, including the European Union, Japan, Latin America, the USA and China.[28–32]

In an animal combined embryo–foetal and prenatal and postnatal development study with monkeys that received belimumab by intravenous administration, there was no evidence of foetal harm nor pregnancy loss rates, with exposures approximately 9 times (based on intravenous administration) and 20 times (based on subcutaneous administration) the exposure at the maximum recommended human dose.[29] However, there was evidence of reductions of immature and mature B-cell counts; while foetal B-cell counts decreased after in utero exposure to 5 and 150 mg/kg of belimumab every 2 weeks during pregnancy, the B cells of infant monkeys fully recovered by 3 months of age.[29 33]

Here, we present birth defect and pregnancy loss data from belimumab clinical trials, the Belimumab Pregnancy Registry (BPR), and postmarketing/spontaneous reports in women with SLE exposed to belimumab prior to or during pregnancy.

METHODS

Data on birth defects and pregnancy loss (miscarriage or stillbirth) with belimumab exposures prior to or during pregnancy were collected from belimumab clinical trials, the BPR and postmarketing/spontaneous reports from the Argus database (which included searches of the US Food and Drug Administration Adverse Event Reporting System and EudraVigilance databases) up to 8 March 2020.

Clinical trials

Although pregnant women were excluded from GSK-sponsored belimumab phase III trials, if pregnancy inadvertently occurred, the patient was withdrawn, but outcomes were monitored for the remainder of gestation. The exception was the phase IV Belimumab Assessment of Safety in SLE (BASE) trial (GSK Study BEL 115467, NCT01705977), where pregnant women could continue on-study at the discretion of the investigator. Investigators were required to report pregnancies to GSK within 24 hours–2 weeks of learning of the pregnancy. Adverse pregnancy outcomes, including birth defects, were reported as serious adverse events. However, because the trials were not designed to study pregnancy outcomes, pertinent variables were not routinely collected (eg, confounding information, antiphospholipid antibodies and factors associated with birth defects). Duplicate pregnancy cases, cases in which the sperm or egg donor was exposed to belimumab and cases where the male partner of the pregnant woman was exposed to belimumab preconception or during pregnancy were excluded from clinical trial cumulative counts. Eighteen belimumab trials were included in this summary (online supplemental table 1). Trial data were combined and summarised as one dataset for belimumab and placebo treatment arms, for all pregnancies ending in live birth (for birth defect summaries) or all pregnancies with known outcomes excluding elective terminations (for pregnancy loss summaries).

Belimumab Pregnancy Registry

The BPR (GSK Study BEL114256, NCT01532310) is a global, multicentre observational cohort study collecting data from individuals with SLE exposed to commercially available belimumab up to 4 months before and/or during pregnancy.[34 35] Individuals self-enrolled and were categorised into a prospective cohort (if they enrolled before the end of the pregnancy) or a retrospective cohort (if they enrolled after the pregnancy outcome occurred).

The primary objective of the BPR was to evaluate birth defects in women with SLE exposed to belimumab using the Metropolitan Atlanta Congenital Defects Program criteria[36] and/or the European Surveillance of Congenital Anomalies criteria.[34 35 37]

Secondary objectives were to evaluate the number of miscarriages, live births (including preterm birth and births of infants classified as small for gestational age), stillbirths, elective terminations and infant outcomes through 12 months of age. Only birth defects and cases of pregnancy loss that were miscarriages or stillbirths have been included in this summary.

Belimumab exposure timing, SLE disease activity and concomitant medications, where available, were reported at registration, at the end of the second trimester and at the time of pregnancy outcome.

Birth defects were reviewed by the study Birth Defect Evaluator to assess defect classification, exposure timing with outcome and potential confounding factors. With respect to pregnancy loss, the BPR defines miscarriage as foetal death or expulsion of products of conception prior to 20 weeks gestation; stillbirths were defined as foetal death occurring at 20 weeks of gestation or greater or for a fetus weighing ≥500 g if gestational age was unknown. Additionally, the BPR Scientific Advisory Committee, comprising the Birth Defect Evaluator and independent experts in SLE, paediatrics and obstetrics, reviewed and interpreted the cumulative data primarily from the BPR but also across the other datasets included in this report. This summary includes data collected between the start of the BPR on 16 July 2012 and 8 March 2020.

Postmarketing/spontaneous reports

The GSK worldwide clinical safety database Argus, a postmarketing reporting system, was searched for postmarketing/spontaneous reports describing pregnancy or lactation with belimumab on 8 March 2020. Clinical trial and BPR cases, duplicate pregnancy cases, cases in which the sperm or egg donor was exposed to belimumab, and cases where the male partner of the pregnant woman was exposed to belimumab preconception or during pregnancy were excluded from the spontaneous report cumulative counts. The remaining reports were then further assessed for pregnancy outcomes of live birth with a birth defect and for pregnancy losses.

Statistical analysis

Due to small sample sizes, limitations related to capture of complete information, the heterogeneity of the data sources and the presence of confounding factors, only cumulative numbers are reported for each of the individual data sources. Birth defect and pregnancy loss data are presented separately throughout for each data source. Ad hoc 95% CIs for the proportion of BPR cases with birth defects or pregnancy loss were calculated using the Wald method (simple asymptotic) without continuity. No statistical testing was performed; other data were summarised descriptively.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Summary of sources

A total of 586 pregnancy reports were identified across 18 clinical trials (n=181 belimumab+ST, n=28 placebo+ST), the BPR (n=57 prospective, n=10 retrospective belimumab +ST) and from postmarketing/spontaneous reports (n=310 belimumab+ST) outside of the BPR (table 1). Pregnancies with known outcomes excluding elective terminations are summarised herein: 126 were identified in clinical trials (n=110 belimumab, n=16 placebo); 56 (n=48 prospective, n=8 retrospective) were identified in the BPR; and 137 were postmarketing/spontaneous reports, with a collective total of 319.

Birth defects and pregnancy losses in belimumab clinical trials

Birth defects: belimumab+ST (n=4/72), placebo+ST (n=0/9)

Of 110 pregnancies with known outcomes excluding elective terminations in women exposed to belimumab during pregnancy in belimumab clinical trials, there were 72 pregnancies ending in live births, and birth defects were identified in four (5.6%) (tables 1 and 2). Two infants from the four pregnancies had more than one birth defect (table 2). In three cases, the investigator was of the opinion that the defect was unlikely to be associated with belimumab exposure; for the case of bilateral enlarged kidneys with severely abnormal function, the investigator indicated that the event was possibly related to belimumab. Investigators are required to mention if they find the association of an adverse event is likely or unlikely to be related to the investigational product. Foetal abnormalities were detected sonographically in two of these cases and abnormalities were not identified in prenatal testing in two cases. Patient characteristic data for the four women from a post hoc summary are shown in table 3. All four patients received prednisone and hydroxychloroquine (table 3).

There were no cases of birth defects reported in women with live births exposed to placebo (n=9).

Pregnancy loss cases: belimumab+ST (n=35/110) and placebo+ST (n=7/16)

Pregnancy loss occurred in 31.8% (n=35) of pregnancies with known outcomes excluding elective terminations in women receiving belimumab and 43.8% (n=7) in those receiving placebo (table 1). None of the pregnancy losses in the belimumab group and one in the placebo group were associated with a birth defect.

Patient characteristic data from a *post hoc* summary are shown in table 3. For all 27 cases of belimumab exposure in the first trimester only, the pregnancy losses occurred within the first trimester. For the one woman who reported belimumab exposure during the first, second and third trimesters, the pregnancy loss occurred within the third trimester. The most common concomitant medications of interest were corticosteroids, hydroxychloroquine and azathioprine (table 3). In eight cases of belimumab exposure, a concomitant medication (a pregnancy category D or X drug; methotrexate, MMF, azathioprine, enalapril, amlodipine or tretinoin) was thought to be likely causative of the pregnancy loss. For 22 cases of belimumab exposure, an alternative diagnosis or concurrent disease was thought to be the most likely cause of the pregnancy loss.

Birth defects and pregnancy losses in the BPR

Pregnancies with known outcomes excluding elective terminations were reported in 56 women who enrolled in the BPR (table 1); of these, 50 pregnancies ended in live births (46 in the prospective cohort and four in the retrospective cohort).

Birth defects: belimumab+ST, prospective cohort (n=10/46); belimumab+ST, retrospective cohort (n=0/4)

Of the 46 pregnancies ending in live births (including two sets of twins) within the prospective cohort, 10 were associated with a birth defect (21.7%, ad hoc 95% CI 9.8% to

Table 1 Summary of pregnancies, birth defects and pregnancy loss recorded in clinical trials, the BPR and postmarketing/spontaneous reports to 8 March 2020

	Clinical trials*		BPR		Postmarketing/spontaneous reports
Outcomes	Belimumab+ST	Placebo+ST	Belimumab+ST, prospective cohort†	Belimumab+ST, retrospective cohort‡	Belimumab+ST
Total number of pregnancies, N	181§	28	57	10	310
Lost to follow-up/unknown, n	13	3	4	0	140
Ongoing, n	1	0	5	0	27
Known outcome, n	167	25	48	10	143
Pregnancies with known outcomes excluding elective terminations, N	110¶	16	48	8	137¶
Pregnancy loss, n (%)	35/110 (31.8)	7/16 (43.8)	2/48 (4.2) (95% CI 0.0% to 9.8%)**	4/8 (50.0)	43/137 (31.4)
Miscarriage with no apparent birth defect, n††	33	5	2	4	40
Miscarriage with birth defect, n††	0	1	0	0	1
Stillbirth with no apparent birth defect, n‡‡	2	1	0	0	1
Stillbirth with birth defect, n‡‡	0	0	0	0	1
Total number of pregnancies ending in live births, N§§	72	9	46	4	92
Pregnancies with live infant with birth defect, n (%)	4/72 (5.6)	0/9	10/46 (21.7) (95% CI 9.8% to 33.7%)**	0/4	1/92 (1.1)
Pregnancies with live infant with no apparent birth defect, n	68	9	36	4	91

*Post hoc summary of double-blind (completed) and open-label (completed/ongoing) phases of clinical studies and NCT03312907, where all arms include belimumab treatment. The following clinical trials were included: NCT01345253, NCT01649765, NCT01597622, NCT01705977, NCT01632241, NCT01894360, NCT03312907, NCT04136145, NCT00410384, NCT00424476, NCT00724867, NCT00732940, NCT00712933, NCT01484496, NCT01597492, NCT00071487, NCT01639339 and NCT00583362.
†Women who enrolled in the registry before the end of pregnancy regardless of known normal or abnormal prenatal test results.
‡Pregnancy ended before enrolment or at the time of first contact with the registry.
§Includes two pregnancies in healthy volunteers (one lost to follow-up and one ended in elective termination).
¶Ectopic and molar pregnancies are included (three in the clinical trials and two in the postmarketing/spontaneous reports); those were not considered pregnancy losses.
**95% CIs were calculated in PASS 2022 V.22.0.2 (ncss.com/software/pass) by ad hoc analysis based on the Wald method (simple asymptotic) without continuity correction.
††Defined as pregnancy loss before the 22nd week of pregnancy; however, this can vary by region and data source. The BPR defines pregnancy loss occurring <20 weeks as miscarriage.
‡‡Defined as pregnancy loss from/after the 22nd week of pregnancy onwards; however, this can vary by region and data source. The BPR defines pregnancy loss ≥20 weeks as stillbirth.
§§There were four twin pregnancies (two BPR and two postmarketing) all ending in live births. Birth defect was diagnosed in one (BPR) of these eight infants. Outcomes reported are per pregnancy and not per infant.
BPR, Belimumab Pregnancy Registry; ST, standard therapy.

Table 2 Cases of birth defects in patients receiving belimumab in clinical trials, the BPR and postmarketing/spontaneous reports

Cumulative count of reported cases	Reported defect	The event fulfils MACDP* criteria?	EUROCAT classified defect?†	Additional considerations
Clinical trials‡				
1	Microcephaly	NP	NP	–
	Atrioventricular septal defect	NP	NP	There is no reason to predict an IgG antibody would affect interventricular septum development (which completes by 7 weeks in humans) because belimumab is highly specific for B-lymphocyte stimulator which binds to receptors primarily localised to B lymphocytes and because there is very little placental transfer of IgG antibodies during the first trimester.[55]
	Unbalanced translocation, involving chromosomes 11 and 13	NP	NP	Unbalanced translocation involving chromosomes 11/13 is not plausibly linked to belimumab because it is not expected that a monoclonal IgG antibody would interact with DNA or chromosomal material
2	Bilateral enlarged kidneys with severely abnormal function	NP	NP	Oligohydramnios, ambrisentan use
	Positional deformities of the head and extremities	NP	NP	–
3	Dandy-Walker syndrome	NP	NP	–
4	Mild pulmonic stenosis (valvular with no intra-atrial shunt)	NP	NP	–
BPR				
1	Bilateral clubfoot	Yes	Yes	Can occur due to mechanical factors that take place within the pregnancy
2	Non-descending testis	Yes	No	May not have involved belimumab exposure during the critical window of development
3	Very mild Ebstein's anomaly of the tricuspid	Yes	Yes	–
4	Congenital heart block	Yes	No	Confounded by neonatal lupus with presence of anti-Ro/SSA and anti-La/SSB antibodies
5	Small ventricular septal defect	Yes	Yes	Described as tiny atypical ventricular septal defect and muscular
	Congenital hydronephrosis	Yes	Yes	–
6	Low-lying conus medullaris	Yes	Yes	–
	Pelviectasis	Yes	No	–
7	Positional plagiocephaly	Yes	No	Can occur due to mechanical factors that take place within the pregnancy
	Positional torticollis	Yes	No	Can occur due to mechanical factors that take place within the pregnancy
8	Small fenestrated atrial septal defect	ED§	Yes	Prenatal testing prior to enrolment with abnormal results
9	Severe Arnold-Chiari type II malformation	Yes	Yes	Enrolled in third trimester, prenatal testing done prior to enrolment but results unknown
10	Ankyloglossia	Yes	No	–
Postmarketing/spontaneous reports				
1	Extrarenal pelvis	NP	NP	Sibling with a cardiac defect reported separately and included in this report; this presents a potential for a reporting bias and/or an underlying genetic predisposition

*Inclusive of birth defects that are tracked by MACDP via the CDC/BPA 6-digit code defect list. Cases were also considered defects if the infant or foetus had two or more conditional defects. MACDP classification analyses were not performed for the cases from clinical trials and postmarketing/spontaneous reports.
†Inclusive of birth defects classified by EUROCAT (eurocat-network.eu/), coded using ICD-10 with a BPA 1-digit extension. EUROCAT classification analyses were not performed for the cases from clinical trials and postmarketing/spontaneous reports.
‡Data shown for belimumab treatment arms only.
§Single EDs within an infant were not considered to be birth defect cases.
BPA, British Paediatric Association; BPR, Belimumab Pregnancy Registry; CDC, Centers for Disease Control and Prevention; ED, exclusionary defect; EUROCAT, European Surveillance of Congenital Anomalies; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; MACDP, Metropolitan Atlanta Congenital Defects Program; NP, not performed; SSA, Sjögren's syndrome-related antigen A; SSB, Sjögren's syndrome-related antigen B.

33.7%), while no birth defects were reported in the retrospective cohort (n=0/4) (table 1). Patient characteristic and concomitant medications of interest data from an ad hoc summary are shown in table 3.

The birth defects within the 10 live birth pregnancies ranged in type and severity according to organ system. Three of the 10 live birth pregnancies had more than one birth defect reported (table 2).

Nine women (90%) had prenatal testing prior to enrolment in the BPR; one had an abnormal result (infant with atrial septal defect) and another case where results were not available (Arnold-Chiari type II malformation) (table 2). All 10 pregnancies resulting in birth defects had prenatal testing results post enrolment in the BPR. Among these, two defects were detected prenatally (bilateral clubfoot and congenital heart block), and one defect (hydronephrosis) was suspected by ultrasound or abnormal prenatal screening post enrolment.

Table 3 Patient characteristics and concomitant medications of interest from belimumab clinical trials (post hoc summary) and the BPR (ad hoc summary)

	Birth defects	Pregnancy loss	
	Belimumab	Belimumab	Placebo
Clinical trials*	n=4	n=35	n=7
Mean (SD) age at enrolment (years)	27.5 (4.51)	28.6 (5.29)†	32.0 (5.48)
Mean SLEDAI at baseline (SD)	11.0 (7.75)	9.2 (4.80)‡	8.4 (1.81)
Trimesters of exposure, n (%)			
First trimester only	1 (25)	27 (77)	3 (43)
First and second trimesters	3 (75)	7 (20)	4 (57)
First, second and third trimesters	0	1 (3)	0
Prednisone use >10 mg/day, n (%)	–	12 (34)	2 (29)
Concomitant medications of interest, n (%)			
Azathioprine	0	6 (17)	2 (29)
Enalapril	0	4 (11)	0
Hydroxychloroquine	4 (100)	18 (51)	2 (29)
Lisinopril	0	2 (6)	0
Losartan	0	3 (9)	0
Methotrexate	0	2 (6)	0
Methylprednisolone	0	4 (11)	0
Mycophenolate	0	4 (11)	0
Corticosteroids: Prednisone/meprednisone/prednisolone	4 (100)	21 (60)	3 (43)
Tretinoin	0	1 (3)	0
aCL baseline status, n (%)			
Baseline status data available		13	6
aCL status positive at baseline		5 (39)	0
BPR	n=10	n=6	–
Mean (SD) age at enrolment (years)	34.2 (3.2)	34.0 (3.4)	–
Earliest belimumab exposure, n (%)			
Preconception	9 (90)	5 (84)	–
First trimester only	1 (10)	1 (17)	–
Last belimumab exposure, n (%)			
First trimester	2 (20)	0	–
Second trimester	6 (60)	0	–
Postpartum	2 (20)	6 (100)	–
Concomitant medications of interest, n (%)			
Antimalarials	9 (90)	3 (50)	–
Immunosuppressants			
Azathioprine	2 (20)	0	–
Cyclosporin	1 (10)	1 (17)	–
Methotrexate	1 (10)	1 (17)	–
MMF	0	1 (17)	–
Corticosteroids	6 (60)	3 (50)	–
Epilepsy medication	1 (10)	0	–
NSAIDs	2 (20)	1 (17)	–
Folate	7 (70)	2 (33)	–
ACE inhibitors	0	0	–
Heparin	2 (20)	0	–
Aspirin	3 (30)	1 (17)	–
Calcium channel blockers	0	1 (17)	–
Beta blockers	0	1 (17)	–

*Other concomitant medications in the birth defects group include, but are not limited to, prochlorperazine, zolpidem, amlodipine, furosemide and ambrisentan (all n=1). Relevant concomitant medications were teratogens, medications associated with pregnancy loss, medications indicating severe or refractory diagnosis or acetylsalicylic acid/warfarin.
†N=34.
‡N=33.
aCL, anticardiolipin; BPR, Belimumab Pregnancy Registry; MMF, mycophenolate mofetil; NSAID, non-steroidal anti-inflammatory drug.

Pregnancy loss cases: belimumab+ST, prospective cohort (n=2/48) and belimumab+ST, retrospective cohort (n=4/8)

Within the prospective cohort, pregnancy loss occurred in 4.2% (n=2 miscarriages, ad hoc 95% CI 0.0 to 9.8%) of the 48 women with known pregnancy outcomes excluding elective terminations (table 1). Of the two women in the prospective cohort who had a miscarriage, one reported not having any prenatal testing prior to enrolment, and no antiphospholipid test, physician global assessment or Systemic Lupus International Collaborating Clinics/ACR Damage Index data were available for both women. None of the pregnancy losses were associated with a birth defect.

Half (n=4/8) of the women from the retrospective cohort with a known pregnancy outcome excluding elective terminations had a pregnancy loss (all miscarriages) prior to BPR enrolment (table 1). One patient with known anticardiolipin (aCL) and lupus anticoagulant (LAC) test data was aCL negative and LAC positive; aCL and LAC data were not known for all other cases. None of the pregnancy losses were associated with a birth defect.

Patient characteristic data from an ad hoc summary are shown in table 3. None of the six women with a pregnancy loss from both BPR cohorts had a history of gestational diabetes, pre-eclampsia, eclampsia or haemolysis, elevated liver enzymes and low platelets syndrome. The most common concomitant medications of interest during pregnancy among the six women were corticosteroids (n=3, all retrospective cases) and antimalarials (n=3, two prospective and one retrospective case) (table 3).

Birth defects and pregnancy loss in postmarketing/spontaneous reports

Known outcomes excluding elective terminations were available for 137 postmarketing or spontaneous reports of pregnancies outside of the BPR in women exposed to belimumab.

One stillbirth and one miscarriage case had a birth defect (table 1). A total of 92 pregnancies ended in live births (including two twin pregnancies), of which 1 (1.1%) pregnancy reported a birth defect (table 1). Pregnancy losses were reported in 43 (31.4%) of the 137 pregnancies with known outcomes, excluding elective terminations (table 1). Confounder analysis was not performed for these postmarketing/spontaneous report cases due to lack of documentation.

DISCUSSION

This report summarises the available data on birth defects and pregnancy loss (miscarriage or stillbirth) in women exposed to belimumab during pregnancy from three available data sources up to 8 March 2020. However, limitations in the data sources used in the present summaries (discussed further) prevented quantitative comparisons of the prevalence and risk of birth defects and pregnancy loss in the pregnancies of belimumab-exposed women with SLE. Furthermore, differences in study populations and timing, diagnostic capabilities, information on SLE severity, clinical factors, concomitant medications, comorbidities and inconsistent definitions of birth defect preclude comparisons between our data and the limited published literature.

SLE and some SLE therapies are associated with birth defect and pregnancy loss. The risk of birth defects in infants of women with SLE is higher than in the general population.[5–7 38] Detailed anatomy ultrasound scans, foetal echocardiography and serial scans are recommended for pregnant individuals with SLE due to increased risks of congenital heart block and foetal growth restriction. Over the past decade, advances in ultrasound technology have enhanced the ability to detect malformations in utero and after birth.[39–41] Estimates of pregnancy loss among women with SLE are ~20% (range across 44 studies: 2.9%–52.6%; see online supplemental file 1), with estimates increasing for those with a longer duration of disease.[42–45]

Available data on belimumab use in pregnant women are insufficient to determine whether there are drug-associated risks for birth defects.[29] Current prescribing information recommends use during pregnancy only if the potential maternal benefit justifies the potential foetal risk.[29] The European Alliance of Associations for Rheumatology and the British Society for Rheumatology advise caution for belimumab treatment during pregnancy,[18 46] and discontinuation once pregnancy is confirmed is recommended by the ACR.[20] These recommendations are based on a lack of data on the effect of belimumab on pregnancy outcomes. Small studies have not identified birth defects with belimumab: a recent real-world study of 13 patients exposed to belimumab during pregnancy in Taiwan reported no birth defects among 11 live births.[47] Similarly, a study of 13 pregnancies of women with SLE exposed to belimumab across three Italian centres reported no defects among 12 live births.[48]

The pregnancy loss results of this summary are a continuation of a previous belimumab safety evaluation published in 2013, in which Wallace and colleagues reported 13 pregnancy losses out of 44 pregnancies with known outcomes (29.5%) in patients receiving belimumab and three pregnancy losses out of six pregnancies (50.0%) in those receiving placebo.[49] These data are included within the current summary.

Consistent with SLE treatment recommendations, the most common concomitant medications across data sources were antimalarials and corticosteroids. The use of these medications is generally considered safe during pregnancy.[1 12 13] Immunosuppressants were also reported for many pregnancies, of which azathioprine was the most common. This is consistent with evidence that suggests certain immunosuppressant medications should be avoided during pregnancy, including MMF, cyclophosphamide and methotrexate, whereas azathioprine use is considered safe at the minimum effective dose.[1 12 13]

There are several limitations to the data used in this summary. The data presented are from various sources with different lengths of belimumab exposure; the clinical trials and postmarketing/spontaneous reports were not specifically designed to assess birth defects nor pregnancy loss and variables potentially impacting pregnancy outcomes were not generally collected in the clinical trials. The impact of SLE disease activity may confound our findings since various adverse pregnancy outcomes are more frequent in SLE pregnancies where disease is more active.[3] This report had insufficient information to determine an association between the timing of belimumab exposure and occurrence of malformations, particularly since some of the observed malformations are associated with other factors (eg, congenital heart block is linked to the presence of maternal anti-Ro/SSA and anti-La/SSB autoantibodies).[9 50] SLE treatment commonly includes immunosuppressants, which can increase the risk of infection; some infections (eg, maternal rubella virus and cytomegalovirus infections) can be teratogenic,[51] although no infections were captured across these data sources. Furthermore, the use of pregnancies ending in live births as the denominator for birth defects likely overestimated the true defect prevalence.

We cannot provide informed recommendations on the use of belimumab during pregnancy owing to insufficient numbers of observed pregnancies, lack of suitable unexposed groups for comparisons, missing information, presence of confounding factors and insufficient methodology to examine birth defects and pregnancy losses, which prevented full statistical analysis.

Understanding the effects of risk factors associated with foetal loss during pregnancy requires complete data capture from conception; as most data used in this report did not collect Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores at the time of conception and at pregnancy loss, our summaries could not accurately assess the frequency of SLE flares during pregnancy. In the clinical trials and BPR, aCL antibody data were only available for approximately half of pregnancy cases, and LAC data were not available. In addition, women voluntarily enrolled in the BPR, and as such may not be representative of all belimumab-exposed SLE individuals, possibly being more motivated and/or having higher pregnancy risks than those who did not volunteer.[52–54] Other limitations include the BPR not having a sufficiently powered control group of pregnant women unexposed to belimumab within the prospective cohort, which may have biased this cohort toward a higher rate of belimumab-related events. Lastly, spontaneous reports are more likely to capture negative rather than positive outcomes, frequently lack the documentation necessary to ascertain causality and are difficult to interpret given the high baseline risk of pregnancy loss in patients with SLE. As such, data should be interpreted with caution.

CONCLUSIONS

We present a summary of data across several sources reporting birth defects and pregnancy loss after maternal exposure to belimumab. Given the limitations of the data, birth defect and pregnancy loss that occurred following belimumab exposure could be presented only descriptively. Increased rates of patient enrolment into pregnancy studies and enhancing quality of data collection in pregnancy studies would allow for better evaluation of birth defects and pregnancy loss risks after maternal exposure to treatment.

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