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Dilemma of belimumab therapy (dis) continuation during pregnancy: Results of a retrospective study in eudravigilance

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Abstract

Introduction: The first biologic authorized for systemic lupus erythematosus (SLE) up to this date, belimumab, is currently not recommended for use during pregnancy due to lack of data. Provided that the health of the child begins with the health of the mother, pregnant patients face the dilemma of cessation or continuation of belimumab. If belimumab is stopped, there will be a risk of SLE flare and its consequences for the mother and the foetus. Continuation is also not optimal because of the lack of knowledge on safety for use during pregnancy.

Aim: To compare the reported foetal outcomes in SLE patients who stopped scheduled belimumab within the first trimester (group A) and those who continued scheduled belimumab during the first trimester or thereafter (group B).

Material and method: All belimumab-exposed pregnancy-related reports were extracted from the EudraVigilance (EV) database until March 11th, 2021. After case review, repeated cases, uninformative reports, non-medical elective abortions and foetal chromosomal abnormalities were excluded. Included pregnancies were divided into two groups (group A and B, as described above). Foetal outcomes were divided into live birth or foetal death (due to miscarriage or stillbirth) and were compared between both groups. Furthermore, neonatal outcomes, such as reporting rates of preterm birth, low birth weight and major congenital malformations were compared.

Results: No statistical difference in foetal death was observed between group A and B (reported numbers (%) = 32 (46.4) and 11 (52.4), respectively). Odds ratio (OR, [95% Confidence Intervals (CIs)]) of foetal death in group B compared to group A was 1.27 [0.48, 3.32]. Reporting rates of preterm birth and low birth weight were higher – though not statistically different – in group A.

Conclusion: The positive results of our study are supportive for the continuation of belimumab during pregnancy. Since the analysis is based on spontaneous reports/retrospective data, additional studies are needed to confirm the results.

Keywords

Systemic lupus erythematosus, belimumab, pregnancy, EudraVigilance database

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Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease. It is estimated that SLE is 10 times more common in women. The onset of the disease is generally at child-bearing age.[1] Approximately 30% of women using conventional SLE treatment will have high disease activity during pregnancy; this will increase to 50% when these treatments are discontinued. The risk of flare is even higher in women with active SLE before conception.[2] Active SLE and nephritis due to SLE contribute to poor pregnancy outcomes and higher morbidities and mortalities in the

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mothers and their foetuses.[3] Limited treatment options are available for the management of SLE during pregnancy, especially for the treatment of SLE nephritis. Corticosteroids, azathioprine, hydroxychloroquine, ciclosporin and tacrolimus are considered safe treatments.[4,5] However, these treatment options may still not be sufficient in patients poorly responsive to conventional therapies or patients who suffer from nephritis.[6]

Belimumab is a recombinant human IgG1λ monoclonal antibody, which inhibits the B-cell activating factor. It is the first biologic approved for the treatment of active SLE.[7] Recent studies show that belimumab is also effective for the treatment of lupus nephritis.[8] Despite authorization in 2011, belimumab is still not recommended for use during pregnancy because of the lack of data.[9] Provided that the health of the child begins with the health of the mother, women using belimumab who wish to conceive or have unplanned pregnancies face the dilemma of stopping or continuing the treatment. In patients with high SLE activity, cessation of belimumab, can lead to a flare.[10] A flare-up of SLE can be harmful to both the mother and the foetus. On the other hand, the consequences of belimumab continuation during pregnancy are currently unknown.[9] Therefore, there is a need to investigate the safety profile of belimumab during pregnancy.

Available sources of information to come to a weighted decision on the use of drugs during pregnancy include pharmacovigilance databases.[11] These include case reports from the literature, clinical trials, and spontaneous reports. Spontaneous reports are suspicions of Adverse drug reactions (ADRs) submitted by healthcare professionals or patients to national pharmacovigilance centres or marketing authorization holders. In Europe, these data are forwarded to the Eudravigilance (EV), a database of the European Medicine Agency (EMA).[12] In addition, pharmaceutical companies submit all serious case reports worldwide.[13] This information may lead to the detection of signals that may have remained unnoticed.[14,15] Data from pharmacovigilance databases has limitations such as heterogeneity of data collection (the lack of collection of denominator information so that the amount of drug use is not known and there is no direct information on disease incidence), under/over-reporting and incompleteness of data and uncertain causal relationship between the suspected drug and reported events. However, it may contribute to a better understanding of the safety profile, especially for newly authorized medications and in special populations (such as pregnant women), who are not included in clinical trials due to ethical concerns. Often additional studies are needed to measure any beneficial effect and estimate the incidences of newly detected ADRs.[16]

This study aims to compare the reported foetal outcomes in SLE patients who stopped scheduled belimumab within the first trimester (group A) and who continued scheduled belimumab during the first trimester or thereafter (group B).

Material and methods

Data source

The EudraVigilance (EV) database is the system for collecting reports of suspected ADRs from patients, clinicians, and pharmaceutical companies, which also includes reports from off-label use such as belimumab treatment during pregnancy. The EV database is active since 2001 and is widely used for signal detection during post-marketing period of medicinal products.[12] The reports of the EV database are mainly from two sources:

1) 'spontaneous reports' are retrospective cases reported by patients, physicians or pharmaceutical companies when a patient experiences an ADR with possible causality from a medicine.
2) 'reports from studies' are prospective cases collected in studies, including patient support programmes. These cases can also include reports without adverse outcomes (here healthy live births).

Comparison with a population outside of the database should be interpreted with caution and of consideration of possible biases (including reporting and information bias).[17,18]

Data collection, inclusion and exclusion

All pregnancy-related ADR reports for belimumab exposure were extracted from the EV database (date assessed on 11-3-2021). Reports are checked for duplicates in EV beforehand as a routine procedure in EV. However, one pregnancy case could contain several reported ADRs under the same unique case report number; these cases are considered only once. In some cases, separated 'linked' reports have been found for a mother and her child. The narratives of both reports were read and merged and counted as one pregnancy case.

After reading the full text (by NG), cases in which the foetal outcome was not reported (for example, ongoing pregnancies) have been categorized as 'uninformative cases' and were excluded. Foetal outcomes with chromosomal abnormalities or elective abortions without medical indication were excluded from further analysis because these cases are unlikely to be therapy-related. Furthermore, cases in which no information on cessation or continuation of belimumab was available were considered missing cases and were excluded as well.

Definitions

Miscarriage was defined as loss of pregnancy before the 20th week of pregnancy. Stillbirth was defined as loss of pregnancy after the 20th week of pregnancy. Categorization of induced termination and miscarriage was based on the reported events and narrative of the reports.

The estimated conception date (ECD) was calculated based on the first day of the last menopausal period (LMP) plus 14 days,[19] unless explicitly stated in the report. To harmonize different approaches in the determination of pregnancy duration, this was calculated based on the time difference between ECD and abortion/birth date of the offspring, if available. Otherwise, 'pregnancy weeks' mentioned in the report was considered as pregnancy duration.

Duration of belimumab exposure during pregnancy was calculated as the time difference (in weeks) between the ECD and last dose plus one half-life of belimumab (≈19 days). If belimumab was continued during the whole pregnancy, the exposure time was calculated as the duration of the pregnancy.

In the EV database, MedDRA (Medical Dictionary for Regulatory Activities) terminology is used for coding ADRs, indications and co-morbidities. MedDRA has hierarchical levels. Most specific and detailed levels (preferred terms (PTs)) are used in EV for reporting ADRs.[20] Data on co-morbidities were noted as MedDRA PT codes (supplementary Tables 1 and 2). If the use of a specific co-medication or the existence of a specific co-morbidity was not mentioned in the report, it was assumed to be absent.

Congenital malformations (CMs) were considered 'major', based on the EUROCAT (European Concerted Action on Congenital Anomalies and Twins) classification.[21,22] The pattern of CMs was reviewed by a clinical geneticist.

The source of the reports was divided into two categories: 'reports from studies' or 'spontaneous reports', based on the coded information in the included reports.

SLE patients were divided into two groups. Those who stopped belimumab therapy shortly before (within 3 months) or during the first trimester (group A), and those who continued scheduled belimumab therapy during the first trimester or thereafter (group B). The treatment with belimumab was considered to be stopped if the next scheduled dose was missed during the pre-conception period or the first trimester based on the information provided in the report. Differences between group A and group B for foetal outcomes (foetal death or live birth) were analyzed. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The reported occurrence of major CM, preterm birth, and low birth weight (LBW) cases were calculated for live births in each group, and ORs [95% CIs] were compared.

Subgroup analysis was performed to investigate the effects by report source (from studies or spontaneous reports) and exposure to co-reported known teratogens on foetal outcome. All of the reported co-medications were included in the final dataset and scanned for teratogenicity based on their official Summary of Product Information (SmPCs).

A p-value of <0.05 was considered statistically significant. The statistical package Stata/SE. V.16.0 for Windows (StataCorp LP, College Station, Texas, USA) was used for statistical analysis.

Results

Initially, 343 pregnancy drug-event reports for belimumab were selected in the EV database. Cases that were reported multiple times (repeated case numbers) (n = 239), uninformative reports (n = 12), elective abortion due to patient's decision (n = 1) and chromosomal abnormalities (n = 1) were excluded. Finally, three cases were excluded since patients' continuation of belimumab was not reported (missing cases).

A total of 87 pregnancies with 90 foetal outcomes were included (including three twin pregnancies). These cases were divided into SLE patients who stopped planned belimumab therapy shortly before or during the first trimester (group A, n = 68), and patients who continued planned belimumab (group B, n = 20). Maternal characteristics are shown in Table 1.

Exposure to concomitant medications aimed for management of SLE, such as corticosteroids, NSAID (non-steroid anti-inflammatory drugs), azathioprine, MTX and mycophenolate mofetil, were higher in group A. This was also observed for exposure to antihypertensive medications and overall exposure to other concomitant medications. Exposure to acetylsalicylic acid and anti-coagulants was higher in group B.

A total of 14 patients were exposed to known teratogenic medications indicated for SLE (MTX and mycophenolate mofetil) in group A and one patient in group B.

Foetal outcomes, viability

Overall, 90 foetal outcomes were reported for 87 pregnancies (two twin pregnancies in group A and one twin pregnancy in group B). The number of foetal death (miscarriage and stillbirth) and live births were compared between the two groups (Table 2). Odds ratio (OR, [95% Confidence Intervals (CIs)]) of foetal death in group B compared to group A was 1.27 [0.48, 3.32].

Neonatal outcomes

Characteristics of the newborns are presented in Table 3 for both groups. Preterm births (gestational age <37 weeks) were reported in 16 live births in group A (43.2%) compared to four preterm births in group B (40%). From live births,

Table 1. Characteristics of study groups.

Patients characteristics		Group A (stopped, n = 67)	Group B (continued, n = 20)	p-value[a]
Age (mean ± SD), years		29.9 (5.1)	30.7 (5.5)	0.61
BMI (mean ± SD.)		27.5 (7.8)	25.4 (7.6)	0.62
Duration of the disease (mean ± SD), years		11.2 (5.9)	9.2 (6.9)	0.57
Duration of belimumab use in total (mean ± SD), years		1.3 (1.4)	1.5 (1.7)	0.70
Belimumab frequency, median (IQR), per X weeks		4 (2, 4)	4 (1, 4)	0.40
Belimumab strength for each dose, median (IQR), milligram		600 (500, 720)	650 (580, 800)	0.49
Duration of belimumab exposure in pregnancy, mean (SD), weeks		3.4 (3)	18.5 (13.3)	**<0.001**
Source of reports from studies: Spontaneous reports		35:32	8:12	0.33
Reported co-existing diseases during pregnancy, n (%)[b]	Patients with any reported co-existing diseases	36 (53.7)	10 (50.0)	0.76
	Hypertension prior to pregnancy	8 (11.9)	1 (5.0)	0.37
	Nephropathies	6 (8.9)	2 (10.0)	0.88
	Infections	10 (14.9)	0 (0.0)	0.06
	Thyroid disorders (hypo/hyperthyroidism)	5 (7.4)	3 (15.0)	0.30
	Arthritis	3 (4.5)	2 (10.0)	0.35
	Antiphospholipid-Ab syndrome	1 (1.5)	2 (10.0)	0.06
Reported active SLE and/or flare during pregnancy, n (%)		4 (6.0)	0 (0.0)	0.26
Singleton: Twin pregnancy		65:2	19:1	0.66
Reported history of previous miscarriages, n (%)		8 (11.9)	3 (15.0)	0.71
Smokers, n (%)		3 (4.5)	1 (5.0)	0.92
Reported alcohol exposure, n (%)		0 (0.0)	2 (10.0)	**0.009**
Reported illicit drug use, n (%)		2 (3.0)	1 (5.0)	0.66
Reported concomitant exposures, n (%)[c]	Exposure to any SLE co-medications other than belimumab	52 (77.6)	14 (70.0)	0.58
	Hydroxychloroquine	44 (65.7)	13 (65.0)	0.95
	Corticosteroids	40 (59.7)	6 (30.0)	**0.020**
	Azathioprine	14 (20.9)	2 (10.0)	0.32
	NSAIDs	7 (10.4)	1 (5.0)	0.45
	MTX	6 (8.9)	0 (0.0)	0.16
	Mycophenolic acid	8 (11.9)	1 (5.0)	0.37
	Acetylsalicylic acid	9 (13.4)	7 (35.0)	**0.029**
	Anti-coagulants[d]	5 (7.4)	4 (20.0)	0.20
	Antihypertensive medications	13 (19.4)	1 (5.0)	0.12

IQR: Interquartile range; MTX: methotrexate; NSAIDs: non-steroid anti-inflammatory drugs.
[a]Significant p-values are bolded. p values larger than 0.01 are reported to two decimal places, those between 0.01 and 0.001 to three decimal places.
[b]Some patients had more than one co-morbidity. Other co-morbidities included: ADHD, acne, asthma, allergy, diabetes mellitus, irritable bowel disease, restrictive pulmonary disease, hepatic disorder, thrombosis, anaemia, anxiety, avascular necrosis, epilepsy, cardiac tamponade, depression, fibromyalgia, morbid obesity, osteoporosis, osteonecrosis, thrombocytopenia and von Willebrand's disease.
[c]Other co-medications included: avobenzone, melanin, immunoglobulin, cefazolin, potassium chloride, cyclosporine, cyclobenzaprine, montelukast, cyclophosphamide, desogestrol, drospirenon, fenticonazole, clotrimazole, hydrocodone, levetiracetam, medroxyprogestrone, metformin, oxycodone, lamotrigine, alprazolam, prochloroperazine, vancomycine, pyroxidine, romiplostim, rituximab levothyroxine, antihistamins and anti-acids (group A); aminocaproic acid, flecanide, hydrocodone, pregabalin, levothyroxine, antihistamins and anti-acids (group B).
[d]In group A, anti-coagulants included: low molecular weight heparin (n = 5, prophylactic). In group B, anti-coagulants included: low molecular weight heparin (n = 3, prophylactic) and edoxaban tosyalte (n = 1, treatment of thromboembolism).

Table 2. Foetal outcomes; n (%).

Foetal outcome	Stopped (group A)	Continued (group B)	Total
Foetal death	32 (46.4)	11 (52.4)	**43 (47.8)**
Live birth	37[a] (53.6)	10[a] (47.6)	**47 (52.2)**
Total	**69**	**21**	**90**

[a]Twin pregnancies are calculated separately for each foetus.

three patients had twin pregnancies (two in group A and one in group B), all resulted in preterm live births. Low birth weight (LBW, <2500 gram) was reported in 9 live births in group A (24.3%) compared to none in group B (0%) (Table 2). The reporting rate of pre-eclampsia was 7 and 2 (20.0% and 22.2%) for group A and group B, respectively. Complete heart block, which is known to be associated with positive anti-Ro antibody SLE during pregnancy,[23] was reported only in one neonate, in group A.

Major CMs were reported for 10 cases (9 live births and one stillbirth) in group A (14.5%) and for two cases (all live births) in group B (9.5%). OR was 0.62 (95% CIs [0.12, 3.08]). Details on the major CMs are presented in Table 4. No specific patterns were detected in group A and group B after reviewing by a clinical geneticist.

Different countries and reporters have different styles in reporting the outcomes to EV. Although the information that can be reported is very extensive, the number of mandatory field is limited. This leads to a great variety in reported information. Therefore, follow-up data such as neonatal cytopenias, responses to vaccinations and neonatal infections, were not completed for all the cases. From reported neonatal infections, four cases belonged to group A and two cases to group B ($p = 0.59$). Neonatal infections were mainly reported in premature neonates or neonates with reported congenital anomalies (see supplementary table 5).

B-cell depletion and low IgM levels were reported only in one neonate (in group A). However, it was considered to be due to rituximab exposure as the mother had experienced a flare after discontinuation of belimumab during first

Table 3. Neonatal characteristics of live born children (including twin pregnancies).

Live births	Stopped (group A); (*n* = 37)	Continued (group B); (*n* = 10)	Total; (*n* = 47)
Gestational age at birth, median (IQR), weeks	37.1 (35.5, 40.0)	38.2 (36.4, 39.1)	**37.6 (36.0, 39.4)**
Weight, median (IQR), grams	2749 (2268, 3200)	2975 (2700, 3175)	**2835 (2406–3175)**
Preterm birth[a]; *n* (%)	16 (43.2)	4 (40.0)	**20 (42.5)**
Low birth weight[a]; *n* (%)	9 (24.3)	0 (0.0)	**9 (19.4)**

IQR: interquartile range.
[a]Preterm birth: gestational age at birth <37 weeks; low birth weight: birth weight under 2500 grams.

Table 4. Major congenital malformations (*n* = number of pregnancies per group); Marked cases have been exposed to co-reported teratogens.

Major congenital malformation	Stopped (group A); (*n* = 69)	Continued (group B); (*n* = 21)
CNS anomalies (*n*)		
	Arnold-Chiari malformation type I (1)	
	Hydrocephalus[a] (1)	
Cardiovascular anomalies		
	ASD + patent ductus arteriosus (1)	Ebstein's anomaly + patent ductus arteriosus (1)
	VSD + patent foramen ovale[b] (1)	
Multiple malformations		
	Pyelocaliectasis + spinal cord anomaly[b] (1)	Hydrops fetalis + torticollis (1)
	Dandy-walker syndrome + unspecified cardiac anomaly (1)	
	Mega cisterna magna + patent foramen ovale (1)	
	Positional plagiocephaly + rectal fistula[c] (1)	
	Kidney enlargement + short stature + rotund torso (1)	
	VSD + hydronephrosis (1)	
Total, *n* (%)	**10 (14.5%)**	**2 (9.5%)**

ASD: Atrial septal defect; VSD: ventricular septal defect.
[a]Placental insufficiency resulted in stillbirth.
[b]Both exposed to methotrexate.
[c]In premature newborn, twin pregnancy.

trimester and got rituximab treatment at second trimester (last reported rituximab infusion at 21st week of gestation). No data were available on neonate's vaccination response from included reports.

Discussion

Analysis of the EV database showed that in cases where belimumab was continued during pregnancy, the rate of foetal death did not increase as compared to cases where belimumab was stopped before or during the first trimester. The data do not provide evidence that belimumab increases the risk of foetus harm.

The decision to continue the use of belimumab during pregnancy in a patient with SLE can only be elucidated/supported by effectiveness studies. It is known that SLE itself has an impact on maternal and perinatal morbidities. SLE increases the risk of intrauterine foetal death (miscarriage and stillbirth), pre-eclampsia, intrauterine growth retardation and preterm birth.[23] Results from a meta-analysis in eleven studies with a total number of 529,778 participants have shown that the relative risk (RR) of miscarriage is significantly higher in the SLE patients compared to women without SLE (RR: 1.51; 95% CI: 1.26–1.82).[24] Furthermore, in a prospective cohort of 267 pregnancies, Clowse et al. found a 3-fold increase in pregnancy loss if SLE was active during first and second trimester.[25] In another study in 55 patients with pre-existing SLE nephropathy, higher rates of foetal loss were observed if nephritis was active at conception (52.6% versus 30.5% in patients in remission).[26]

About half of SLE patients have measurable disease activity during pregnancy.[27] Yet, limited treatment options are available for pregnant SLE patients. Hydroxychloroquine is currently advised to be used in all SLE patients, regardless of pregnancy status.[28] Besides that, corticosteroids, azathioprine, ciclosporine and tacrolimus also can be used.[28,29] However, sometimes patients do not respond properly to these medications. Unfortunately, some effective treatment options are recommended to be interrupted and avoided if a patient becomes pregnant according to current guidelines. The reason is the lack of safety data on exposure during pregnancy and thereby to the human foetus. Belimumab is one of these medications.[28–30] Belimumab is indicated as add-on therapy in patients with active SLE or lupus nephritis.[9] Both groups are expected to have high-risk pregnancies.[25,26]

Currently, there are very limited published data regarding the use of belimumab during pregnancy. Multiple case reports do not describe any safety concerns.[31–35] Reproductive toxicology studies in cynomolgus monkeys did not show any maternal and foetal adverse effects when relatively high doses of belimumab were used during pregnancy.[36] Due to ethical concerns, it is not possible to conduct experimental studies with medication use in pregnant patients. Therefore, information on exposure during pregnancy after registration of belimumab may shed a light on safety or potential risks. One of the sources of information is to analyze the reports submitted to pharmacovigilance databases, such as EV database. To the authors' knowledge, this is the first study to compare the SLE pregnancy outcomes based on the exposure duration to belimumab.

In this study, we divided patients into two groups: patients who stopped belimumab when pregnancy was revealed or who stopped before their next scheduled dose and patients who decided to continue belimumab as planned. Only one half-life of belimumab was added to calculate the exposure duration. This has not affected the results. Because exposure duration was only a variable considered in the characteristics table (Table 1) and not for categorization to group A or B. Theoretically 50% of the product is still present after one half-life.[9,37] However, the influence of the underlying disorder will likely become more prominent. Pharmacokinetic data shows higher complement levels, anti-Sm, and anti-ribosomal *P* antibodies, and lower reduction of plasma cells in lower exposure.[38] This may also have an impact on pregnancy outcomes.

Foetal death, viability

No statistically significant difference in pregnancy outcomes was observed between patients who continued and patients who stopped belimumab. Nevertheless, the proportion of cases with foetal death is high among both groups (Table 2). This may partially be explained by the fact that belimumab is only indicated as add-on therapy in SLE patients with high disease activity. Therefore, by indication, high proportions of intrauterine foetal death in these patients is anticipated (previous studies report foetal loss between 25% and 52%).[9,24,25] In addition, reporting bias may have played a role as well. Submission criteria of pregnancy reports to the EV database are different between spontaneous reports and reports from studies. During the clinical trials, any pregnancy that occurred should be reported to EV, disregards an adverse or a normal outcome. However, if reporting is spontaneous and not in the context of a clinical study, pregnancy report should be submitted only if an adverse event has occurred.[17,39] Normal outcomes should also be collected, but are not obliged to be submitted in the EV system (risk of under-reporting).

The use of co-medications and the existence of co-morbidities, such as antiphospholipid antibody syndrome (AAS), are important alternative explanations for high rates of miscarriages.[2,40] Due to the nature of data collection in the EV database, these factors may be under-reported in our study. This information might not be mentioned explicitly in the text of the reports. From known teratogens[30] exposure to cyclophosphamide, methotrexate and mycophenolate mofetil was reported in included cases. Information retrieved

from the reports regarding other co-medications and co-morbidities was heterogeneous and could not be further analyzed.

Neonatal outcomes

In a large population-based case-control study in 507 women with SLE, rate of major CMs was 13.6% (adjusted OR = 1.28, 95% CI [1.01, 1.62]).[41] The rate of major CMs in our study is comparable to these results.

After consulting with a clinical geneticist, there was no specific patterns detected regarding the reported major CMs in groups A or B. As explained above, in the collection of data for pharmacovigilance databases, there is a tendency to only report adverse outcomes. Therefore, higher rates are expected compared to the general population. Furthermore, in many member states, there are strict obligations to report any CMs. A relation between the reported CMs and belimumab exposure is considered unlikely.

Overall, 14 (20.2%) foetuses in group A and one (4.7%) foetus in group B were exposed to teratogens (Supplementary Table 3). As expected, higher rates of CMs were observed in group A. This suggests that a correlation between belimumab use and the occurrence of these CMs may be less likely. From 14 teratogen exposed cases in group A, two patients exposed to methotrexate have reported CMs in the foetuses. Ventricular septal defect + patent foramen ovale (n = 1) and pyelocaliectasis + spinal cord anomaly (n = 1) were reported. Both can be associated with methotrexate.[42]

No cases of LBW were observed if belimumab was continued, compared to 9 cases (24.3%) if belimumab was stopped during early pregnancy. This difference may be due to better disease control in patients who continued belimumab therapy. Another reason may be corticosteroid-sparing effects of belimumab. Corticosteroids may increase the risk of LBW.[43] In our study, corticosteroid use was almost 30% lower if belimumab was continued. This is also confirmed in the results of efficacy studies for belimumab in the general SLE population.[44–47]

Limitations

One important factor to be considered in interpreting the results is the limitations due to the collection of data from pharmacovigilance databases. In our study, the origin of the reports was heterogeneous. Around half of the reports were submitted spontaneously, while others were reports from the studies. Spontaneous reports may be inaccurate or incomplete. Normal outcomes may be under-represented in cases with spontaneous reporting origin.[39,48,49]

In this study, the proportion of spontaneous reports vs. study reports was higher in patients who continued belimumab therapy (Table 1). To investigate the further role of origin of the reports (spontaneous of from studies) in the occurrence of foetal death, data was stratified (Supplementary Table 4). Occurrence of foetal death was numerically (but not statistically) higher in spontaneous reports (54.4% versus 40.9%, p-value: 0.76). Because of the tendency of spontaneous reports to report adverse events, the results should be interpreted with caution.[39,48]

Another limitation of this study is the small sample size, which is below the requested 300 to 1000 prospectively followed pregnancies for labelling purposes.[50]

Conclusion

The positive results of our study are supportive for the continuation of belimumab during pregnancy. However, considering the limitations of data collection from pharmacovigilance databases, and in this case small sample size, multiple teratogens in group A and suspicion of important reporting bias, the results should be taken with caution. Belimumab continuation can be considered in the management of women with a high risk of flare and have not responded to other treatments adequately. Further investigations (particularly prospective and more robust data) are needed to confirm an absence of association between belimumab and foetus harm.

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Author's contributions

N Ghalandari: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Project administration. HJMJ Crijns: Writing - Review & Editing, Funding acquisition. RJEM Dolhain: Writing - Review & Editing. JMW Hazes and EP van Puijenbroek: Methodology, Writing - Review & Editing, Supervision.

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Data statement

For the purpose of this study a protocol was submitted and approved by the authorities in European Medicine Agency (EMA).

Stakeholders can access to EudraVigilance data in accordance with Regulation (EU) 2016/679, the General Data Protection Regulation (GDPR) and Regulation (EU) 2018/1725, the EU Data Protection legislation (EU DPR). As a member of the Dutch national medicines regulatory authority (CBG-MEB) and after approving the study protocol, N Ghalandari gained access to EudraVigilance database.

Disclosures

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