Use of Belimumab throughout 2 Consecutive Pregnancies in a Patient with Systemic Lupus Erythematosus

To the Editor:

Effects of belimumab on pregnant patients with systemic lupus erythematosus (SLE) are unknown. To our knowledge, we described the first case of a patient with active SLE who was treated with belimumab throughout her pregnancy[1]. The patient became pregnant again and we describe its successful outcome here.

Ethical board approval for case reports is not required per institution policy. Informed consent was obtained from the patient.

A 41-year-old woman with difficult-to-control SLE (antinuclear antibody–positive, SSA, dsDNA, antigranulocyte antibody–positive, and lupus nephritis) reported to be pregnant again while receiving belimumab. Belimumab was used successfully during her first pregnancy because of contraindications or side effects to azathioprine, mycophenolate, rituximab, and cyclophosphamide (Table 1). Her second conception resulted in a miscarriage, which was because of aneuploidy and was not thought to be because of SLE. Her SLE was in remission for 18 months before her third conception (Table 1). She maintained treatment with belimumab 10 mg/kg, hydroxychloroquine 400 mg, prednisone 5 mg, and low molecular weight heparin. She had intensive monitoring with monthly ultrasound, noninvasive prenatal testing, and fetal echocardiography. Serial testing did not reveal any developmental abnormalities, heart blockage, or aneuploidy. Her SLE was in clinical remission during her pregnancy (Table 1). She had a history of longstanding leukopenia that was monitored and had no infections. Belimumab was successful in controlling all her SLE manifestations apart from her leukopenia. Her belimumab infusion was continued until 33 weeks of gestation. Her non-stress test done at 37 weeks showed a normal fetal heart rate with moderate variability and accelerations. The patient had a planned Cesarean delivery at 39 weeks. A healthy baby boy was born: 19 inches long, head circumference of 14 inches, and weight 7 pounds, 6.9 ounces. He had normal Apgar scores at birth. The baby did not have any evidence of Ebstein anomaly as was noted to be present in the patient's first baby. He did not have any congenital heart blocks despite the positive maternal SSA serology. He did have an extrarenal pelvis and was followed closely by pediatric urology. Belimumab was restarted 3 weeks after the delivery. The patient and baby continue to do well a year later.

Effective management of SLE before conception and during pregnancy has been shown to improve outcomes[2]. A very limited number of medications can be used in SLE without having a potential harmful effect on the baby. Belimumab was successful in achieving good SLE control during both pregnancies in our patient. Her second baby did have an extrarenal pelvis, which is considered a normal anatomic variant[3]. Our patient did have leukopenia prior to the initiation of belimumab and she continued to have grade 3 or grade 4 leukopenia. Leukopenia has been reported in the clinical trials on belimumab[4,5,6], and the cause of our patient's leukopenia is likely a combination of SLE activity and belimumab use. The role of her antigranulocytic antibodies in the development of leukopenia cannot be ruled out.

To our knowledge, there are no human clinical studies available evaluating the use of belimumab in pregnant women. Belimumab crosses the placenta in pregnant monkeys in concentrations that result in reversible pharmacologic activity in fetuses and newborn monkeys[7]. Pregnancy was an exclusion criterion in all belimumab trials. The pooled data from placebo-controlled belimumab studies reported 6 pregnancies in the placebo arm, and there were no live births[4]. Hydroxychloroquine use was 63%, corticosteroid use was 81%, and other immunosuppressant use was 48% in the belimumab group[4].

The Belimumab Pregnancy Registry (BPR)[8] aims to evaluate pregnancy and infant outcomes in women with SLE exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy. As of March 2016, there were 21 participants with confirmed outcomes; 19 were exposed to belimumab within 4 months prior to conception, 1 patient was exposed in the first trimester, and the timing of exposure in the elective termination was not evaluated. There were 17 participants who had live births (1 twin pregnancy; 18 total live births), 1 had elective termination of pregnancy (no apparent congenital anomaly reported), and 3 had spontaneous miscarriages. Four of 18 live births were reported to have congenital anomalies[8,9]. Cumulative data from clinical trials, spontaneous reports, BPR, and postmarketing surveillance have reported a total of 254 pregnancies (Table 2)[9]. Congenital abnormalities reported in live infants of patients exposed to belimumab included Dandy Walker syndrome, bilateral enlarged kidneys, pulmonic stenosis, mild Ebstein anomaly (our patient's first child), unbalanced translocation between chromosomes 11 and 13, bilateral club foot, and ventricular septal defect. The data from the BPR, though limited, demonstrate that patients receiving belimumab can have successful pregnancy outcomes. There is still insufficient evidence to prove the safety of belimumab during pregnancy. Additional data from the BPR and postmarketing surveillance over the coming years will be of value in answering this.

Table 1. Laboratory data from first and second successful pregnancy.

Time	Hb, mg/dl	WBC, per cm^2	Platelet Count, k/cm^2	Serum Creatinine, mg/dl	UPCR, mg/mg	C3, 88–201 mg/dl	C4, 16–47 mg/dl	dsDNA Titer
3 mos before belimumab	11.9	8.2	215	1.12	0.11	62	8	1:80
At initiation of belimumab	11.8	4.0	176	0.89	0.1	73	17	1:40
6 mos after belimumab	11.8	2.6	170	0.77	0.14	73	22	—
12 mos after belimumab	12	2.1	140	0.83	0.25	59	16	—
First trimester, first pregnancy	11.7	1.9	161	0.59	0.14	87	24	1:40
Second trimester, first pregnancy	10.8	1.5	164	0.78	0.28	98	35	1:80
Third trimester, first pregnancy	10.9	2.4	158	0.70	0.19	99	32	1:40
Postpartum, first pregnancy	11.9	0.9	195	0.78	—	73	22	1:80
3 mos before second pregnancy	12.1	1.37	274	0.79	0.12	122	36	1:80
First trimester, ~8 weeks	13.0	1.58	246	0.78	—	—	—	—
Second trimester, ~20 weeks	10.7	1.84	205	0.64	0.15	140	46	—
Third trimester, ~34 weeks	12.0	1.46	175	0.73	0.16	—	—	—
3 weeks postpartum, first belimumab infusion postpartum	12.5	1.74	301	0.75	0.16	—	—	—
6 mos postpartum	12.4	0.97	213	0.68	0.22	140	30	48 (quantitative)
12 mos postpartum	12.9	1.15	203	0.72	—	—	—	—

Hb: hemoglobin; WBC: white blood cell; UPCR: urine protein creatinine ratio.

Table 2. Cumulative pregnancy outcomes from clinical trials, spontaneous reports, postmarketing surveillance, and the Belimumab Pregnancy Registry.

Variables	n
Total pregnancies	254
Lost to followup	45
Total pregnancies with known outcomes	182
Elective termination, no apparent congenital anomaly	48
Total pregnancies with known outcomes excluding elective termination	134
Total live births	90
Live infant with no apparent congenital anomaly	82
Live infant with congenital anomaly	8

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