Monoclonal Antibodies, Systemic Lupus Erythematosus, and Pregnancy: Insights from an Open-label Study

To the Editor:

Controlled clinical trials have revealed modest efficacy for the use of belimumab in the treatment of systemic lupus erythematosus (SLE)[1,2]. Followup of these patients has been published and of the 1458 patients who have received belimumab during phase II and III clinical trials, the most frequent events leading to discontinuation were lupus nephritis and infusion-related reactions[3]. We report herein the status of 47 patients who received open-label belimumab from a single-site cohort of patients whose longterm followup (mean 62 mos) could be ascertained. Pregnancy was found to be an atypical and potentially important reason for drug discontinuation that bears additional scrutiny.

Study design and patient demographics for the first 52 and 76 weeks have been reviewed and published elsewhere[1,2]. Our initial cohort was composed of 55 patients in 2 double-blind, placebo-controlled trials: HGS-1056 and LBSL-02 (Figure 1). Twelve patients withdrew while blinded: 4 were receiving placebo and 8 withdrew because of pregnancy, flares (lupus nephritis, neuropsychiatric lupus), noncompliance, inefficacy, breast cancer, and the need for an exclusionary medication. Withdrawal of these 12 patients and an addition of 4 patients who were transferred from another site yielded a total of 47 patients who received belimumab on open-label extension. Of these, 17 withdrew for reasons including flares (n = 5), pregnancy-related issues (n = 5), and other concerns (n = 7). In patients withdrawing because of flares, 2 were because of lupus nephritis (worsening proteinuria confirmed by renal biopsy) requiring more aggressive therapy, while the remaining 3 were because of concomitant inflammatory arthritis, cutaneous vasculitis, and adult-onset Still's disease.

Of the pregnancy-related issues that arose during the trial, 3 women withdrew because of their desire for pregnancy and 2 were withdrawn because of positive urine pregnancy testing. Subsequently, 2 women experienced miscarriages and 1 delivered a full-term baby, but then developed lupus nephritis that led to a kidney transplant. Of those who withdrew from open-label belimumab for reasons other than pregnancy or flare, 1 developed breast cancer, 2 felt that the belimumab did not provide enough improvement to warrant continuation (inefficacy), 1 developed a concurrent illness (paranoid schizophrenia), 1 experienced a serious adverse event (myocardial infarction), and 2 were withdrawn for noncompliance.

Currently, 64% of the patients at our site are still enrolled in the open-label extension of belimumab therapy. In our cohort, withdrawal because of pregnancy-related issues was as frequent as withdrawals because of flares and greater than any individual "other" reason. Because SLE occurs disproportionately in women of childbearing age, ascertaining the safety of belimumab during pregnancy is of crucial importance.

Belimumab is a recombinant human immunoglobulin G1 monoclonal antibody that inhibits B lymphocyte stimulator, a tumor necrosis factor (TNF) family member that supports B cell maturation and proliferation.

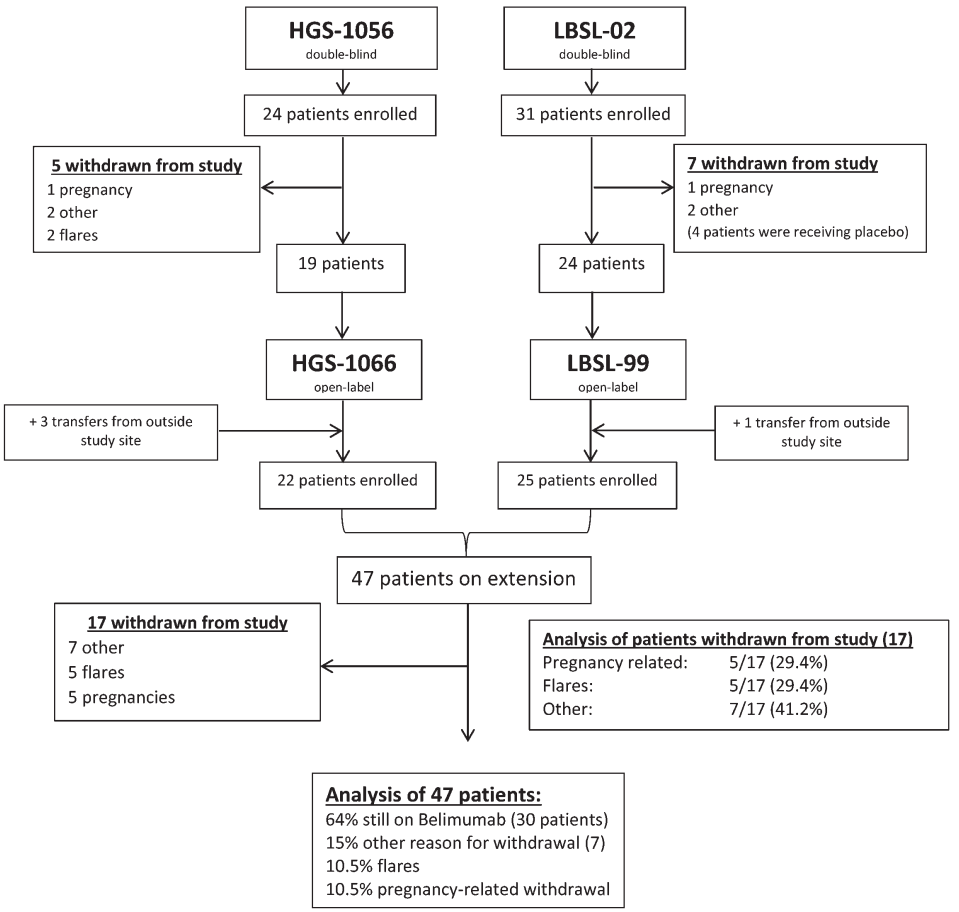

Figure 1. Flow chart depicting 2 double-blind, placebo-controlled trials of belimumab: HGS-1056 and LBSL-02. Initially, our cohort consisted of 55 patients divided between the 2 trials: 24 and 31, respectively. Subsequently, a total of 12 patients were withdrawn and 4 were added, generating a total of 47 patients receiving belimumab on open-label extension.

There is insufficient evidence to prove absolute safety of using biologics such as belimumab during pregnancy given the lack of controlled trials and insufficient human data[4]. In a study where belimumab was given supratherapeutically to pregnant monkeys and followed throughout gestation, effects attributed to therapy were limited to decreased B lymphocytes in the mothers and infants, but demonstrated recovery on cessation of exposure[5]. With regards to humans, it has been shown that passage across the placenta of monoclonal antibody-based TNF inhibitors is not seen in the first trimester, but is notable in the third trimester. Uncontrolled immunologic-mediated disease is a threat to pregnancy; therefore, experts recommend that the drug be stopped only in the third trimester[6]. It is generally not recommended to terminate pregnancy after first trimester TNF-inhibitor exposure without evidence of a congenital anomaly[7].

Data on belimumab in pregnancy from controlled, randomized trials is limited to 95 pregnancies reported as of March 8, 2013, to GlaxoSmithKline (personal communication). Of the reported pregnancies, there were 35 live births without congenital anomaly, 3 live births with congenital anomaly (corresponding with the national average of 3%)[8], 20 elective terminations, 23 spontaneous abortions, 2 stillbirths without congenital anomaly, and 12 ongoing/unknown. Of the 3 congenital anomalies, 1 was because of Dandy-Walker syndrome, 1 was associated with the exposure to a known teratogenic drug, and the third was due to a chromosomal translocation in the mother and could not be attributed to belimumab[9,10].

A pregnancy registry has been established by the manufacturer and we await the results of studies addressing the safety of belimumab in pregnant women. Experts in the field, including those dealing with inflammatory bowel disease as well as rheumatic diseases, tell us that flares of the underlying disease in early pregnancy are the most serious in terms of poor pregnancy outcomes[7]. That said, continuing monoclonal antibody treatment in active disease states may provide direct benefit to the mother and the pregnancy outcome, thereby outweighing a potential risk to the fetus. The frequency of arbitrary drug discontinuations in our data was surprising and a reason to reevaluate policies typically instituted in sponsored clinical trials.

VANEET K. SANDHU, MD, Fellow; DANIEL J. WALLACE, MD, Associate Director; MICHAEL H. WEISMAN, MD, Director, Department of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, California, USA. Address correspondence to Dr. M.H. Weisman, 8700 Beverly Blvd., B131, Los Angeles, California 90048, USA.
E-mail: weisman@cshs.org

REFERENCES

1. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721-31.
2. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918-30.
3. Wallace DJ, Navarra S, Petri MA, Gallacher A, Thomas M, Furie R, et al. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus 2013;22:144-54.
4. Nielsen OH, Loftus EV Jr, Jess T. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. BMC Med 2013;11:174.
5. Auyeung-Kim DJ, Devalaraja MN, Migone TS, Cai W, Chellman GJ. Developmental and peri-postnatal study in cynomolgus monkeys with belimumab, a monoclonal antibody directed against B-lymphocyte stimulator. Reprod Toxicol 2009;28:443-55.
6. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:286-92.
7. Clowse ME. The use of anti-TNFα medications for rheumatologic disease in pregnancy. Int J Womens Health 2010;2:199-209.
8. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep 2008;57:1-5.
9. Peart E, Clowse ME. Systemic lupus erythematosus and pregnancy outcomes: an update and review of the literature. Curr Opin Rheumatol 2014;26:118-23.
10. Powell M, Hill D, Eudy A, Landy H, Petri M. Pregnancy outcomes for systemic lupus erythematosus subjects (SLE) with conception during belimumab intravenous (IV) and subcutaneous (SC) placebo-controlled clinical trials and long term extension trials. Ann Rheum Dis 2014;73 Suppl 2:75-6.

J Rheumatol 2015;42:4; doi:10.3899/jrheum.140952