Safety and Efficacy of Belimumab to Treat Systemic Lupus Erythematosus in Academic Clinical Practices

Joyce S. Hui-Yuen, Arthi Reddy, Jennifer Taylor, Xiaoqing Li, Andrew H. Eichenfield, Liza M. Bermudez, Amy J. Starr, Lisa F. Imundo, Jill Buyon, Richard A. Furie, Diane L. Kamen, Susan Manzi, Michelle Petri, Rosalind Ramsey-Goldman, Ronald F. van Vollenhoven, Daniel J. Wallace, and Anca Askanase

ABSTRACT. ***Objective.*** To evaluate the use and efficacy of belimumab in academic practices. Belimumab is a human monoclonal antibody that inhibits soluble B lymphocyte stimulator and has been approved for the treatment of adults with systemic lupus erythematosus (SLE).

Methods. Invitations to participate and complete a 1-page questionnaire for each patient prescribed belimumab were sent to 16 physicians experienced in SLE phase III clinical trials. The outcome was defined as the physician's impression of improvement in the initial manifestation(s) being treated without worsening in other organ systems.

Results. Of 195 patients treated with belimumab at 10 academic centers, 96% were taking background medications for SLE at initiation of belimumab, with 74% taking corticosteroids. The main indications for initiation of belimumab were arthritis, rash, and/or worsening serologic activity, with 30% of patients unable to taper corticosteroids. Of the 120 patients taking belimumab for at least 6 months, 51% responded clinically and 67% had ≥ 25% improvement in laboratory values. While numbers are limited, black patients showed improvement at 6 months. In a subset of 39 patients with childhood-onset SLE, 65% responded favorably at 6 months, and 35% discontinued corticosteroids.

Conclusion. Our data demonstrate favorable clinical and laboratory outcomes in patients with SLE at 6 months across all racial and ethnic groups, with similar improvement seen among patients with childhood-onset SLE. (First Release November 1 2015; J Rheumatol 2015;42:2288–95; doi:10.3899/jrheum.150470)

Key Indexing Terms:
BELIMUMAB
CHILDHOOD-ONSET SLE
SLE TREATMENT
SYSTEMIC LUPUS ERYTHEMATOSUS

From the Division of Pediatric Rheumatology, Morgan Stanley Children's Hospital of New York-Presbyterian Hospital/Columbia University Medical Center; New York University Langone Medical Center; Division of Rheumatology, New York-Presbyterian Hospital/Columbia University Medical Center, New York; Hofstra North Shore-LIJ School of Medicine, Hempstead, New York; Medical University of South Carolina, Charleston, South Carolina; Temple University School of Medicine, Philadelphia, Pennsylvania; Johns Hopkins University School of Medicine, Baltimore, Maryland; Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; Karolinska University Hospital, Stockholm, Sweden; Cedars-Sinai Medical Center, Los Angeles, California, USA.

Supported by an investigator-initiated award to the Systemic Lupus Erythematosus International Collaborating Clinics from GlaxoSmithKline. Dr. Hui-Yuen is the recipient of a T32 Medical Genetics training grant from the US National Institutes of Health. Dr. Askanase is a consultant for GlaxoSmithKline (< $10,000 in the past 12 months), and Dr. Petri has been a consultant for GlaxoSmithKline.

J.S. Hui-Yuen, MD, MSc, Fellow, Division of Pediatric Rheumatology, Morgan Stanley Children's Hospital of New York-Presbyterian Hospital/Columbia University Medical Center; A. Reddy, BSc, Research Assistant, New York University Langone Medical Center; J. Taylor, MD, Pediatric Resident, Division of Pediatric Rheumatology, Morgan Stanley Children's Hospital of New York-Presbyterian Hospital/Columbia University Medical Center; X. Li, BSc, Research Assistant, Division of Rheumatology, New York-Presbyterian Hospital/Columbia University Medical Center; A.H. Eichenfield, MD, Assistant Professor, Division of Pediatric Rheumatology, Morgan Stanley Children's Hospital of New York-Presbyterian Hospital/Columbia University Medical Center; L.M. Bermudez, MD, Fellow, Division of Pediatric Rheumatology, Morgan Stanley Children's Hospital of New York-Presbyterian Hospital/Columbia University Medical Center; A.J. Starr, MD, Assistant Professor, Division of Pediatric Rheumatology, Morgan Stanley Children's Hospital of New York-Presbyterian Hospital/Columbia University Medical Center; L.F. Imundo, MD, Division of Rheumatology, New York-Presbyterian Hospital/Columbia University Medical Center; J. Buyon, MD, Professor, New York University Langone Medical Center; R.A. Furie, MD, Professor, Hofstra North Shore-LIJ School of Medicine; D.L. Kamen, MD, MS, Associate Professor, Medical University of South Carolina; S. Manzi, MD, MPH, Professor, Temple University School of Medicine; M. Petri, MD, MPH, Professor, Johns Hopkins University School of Medicine; R. Ramsey-Goldman, MD, DrPH, Professor, Northwestern University Feinberg School of Medicine; R.F. van Vollenhoven, MD, PhD, Professor, Karolinska University Hospital; D.J. Wallace, MD, Professor, Cedars-Sinai Medical Center; A. Askanase, MD, MPH, Associate Professor, Division of Rheumatology, New York-Presbyterian Hospital/Columbia University Medical Center.

Address correspondence to Dr. A. Askanase, Division of Adult Rheumatology, New York Presbyterian Hospital, Columbia University Medical Center, 630 W. 168th St., P&S Building, 10th floor, New York, New York 10032, USA. E-mail: ada20@cumc.columbia.edu

Accepted for publication July 28, 2015.

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease of unknown etiology with a heterogeneous range of clinical and serological manifestations. Adding to the complexity of SLE is the unpredictability of flares, or periods of increased inflammatory disease activity, as well as the accrual of organ damage[1,2]. "Standard of care" therapy for SLE includes antimalarials, corticosteroids, immunosuppressives, and cytotoxic agents. These treatments often result in undesired longterm adverse effects and organ damage that are unavoidable because of the essential role of these medications in SLE treatment.

Although the etiology of SLE remains largely unknown, an increased understanding of its immunopathogenesis, in particular B cell–specific mechanisms, has allowed for a focus on targeted immunotherapy. This led to the development and testing of belimumab for SLE and its subsequent approval in 2011 by the US Food and Drug Administration (FDA) for the treatment of adults with active SLE[3]. Belimumab is a fully human, recombinant inhibitor of soluble B lymphocyte stimulator and neutralizes a key cytokine that plays a major role in B cell differentiation, proliferation, and survival[4,5,6]. Two randomized, double-blind, placebo-controlled, multicenter phase III trials (BLISS-52 and BLISS-76) demonstrated improvement in disease activity in patients treated with belimumab and standard-of-care SLE therapy compared to those treated with placebo and standard therapy alone[7,8].

Since the initial belimumab clinical trials, the post-approval clinical experience of patients receiving belimumab at 10 mg/kg/dose every 4 weeks along with standard SLE therapy as well as the practice patterns of academic physicians in clinical settings have received increased attention. Even so, the data are scarce on the use of belimumab in patients with childhood-onset SLE. Childhood-onset is diagnosed prior to the patient's 18th birthday and accounts for up to 20% of all patients with SLE[9]. When compared to adult-onset SLE, childhood-onset SLE has increased disease activity, morbidity, and mortality, often requiring earlier and more aggressive treatment with immunosuppressive medications for disease control[10,11,12,13,14,15,16].

Because of the multitude of challenging characteristics of successful trials, including identifying meaningful outcomes and appropriate patient populations, postmarketing observational studies are often useful in providing supplementary information to trials. The objective of this multicenter study was to analyze the experience with belimumab in academic clinical practices.

MATERIALS AND METHODS

Study design. This is a prospective, multicenter, observational study conducted in 10 large academic SLE clinical practices, 9 of which were in the United States. Approvals to conduct this study were obtained from the institutional review boards of the respective institutions. Sixteen adult rheumatologists experienced in phase III SLE clinical trials were invited to participate, 10 of whom accepted the invitation and completed repeat assessments of patients with SLE treated with belimumab as part of their standard of care. Assessments consisted of a single-page questionnaire per patient completed every 3 months. All investigators who agreed to participate were located in countries where belimumab has received regulatory agency approval (United States and Sweden).

Inclusion and exclusion criteria. All patients were required to have a diagnosis of SLE, have met at least 4 of 11 American College of Rheumatology (ACR) or Systemic Lupus International Collaborative Clinics classification criteria[17,18], and have started treatment with belimumab after approval by regulatory agencies. Exclusion criteria included patients who had previously participated in the belimumab clinical trials, and those who met fewer than 4 ACR classification criteria. We also excluded patients who had severe renal or neuropsychiatric involvement.

Questionnaire. The single-page questionnaire included basic demographic information (e.g., age, sex, race/ethnicity), SLE data [including disease duration, year of diagnosis, serologies, clinical manifestation(s), and concomitant medications], and belimumab information (including start date, clinical response, laboratory response, side effects, and reasons for discontinuation, if appropriate). The questionnaires were completed every 3 months by the treating physician to record longterm clinical patterns of belimumab.

Outcomes. All investigators adhered to the guidelines for 50% improvement as defined by the Responder Index for Lupus Erythematosus and British Isles Lupus Assessment Group, including clinical improvement and at least intent to decrease therapy[19,20] without worsening in any organ systems. This was further defined as the treating physician's impression of a ≥ 50% improvement in the initial manifestation(s) being treated and the ability to taper existing steroid dose by at least 25% of the initial dose for those patients who were taking steroids at the initiation of belimumab. Anti-dsDNA positivity was defined as having an anti-dsDNA level above the normal range; similarly, low complement was defined as having a C3 and/or C4 level below the normal range. Laboratory response was defined as a ≥ 25% improvement in the levels of C3, C4, and/or a 25% decrease in anti-dsDNA antibody levels. Responders were those patients who achieved the outcome measures as defined above; nonresponders were those who did not. Moreover, to be classified as a responder, there could be no worsening in other organ systems.

Data analysis. Descriptive statistics were used to evaluate the baseline characteristics of enrolled patients using Graphpad Prism 6. Every 3 months, clinical and laboratory response data were evaluated using t tests and chi-squared tests where appropriate.

RESULTS

Demographics. A total of 195 patients with SLE treated with belimumab were enrolled, most of whom were female (Table 1), with 29% black and 11% Hispanic. The average disease duration at initiation of belimumab was 11.9 ± 8.1 years among the 151 patients with data available regarding the date of diagnosis. Four patients were antinuclear antibody–negative.

Concomitant medications. Of 195 patients, 7 with adult-onset SLE were not taking any background SLE medications at the time of belimumab initiation (Table 1), while 73% were taking antimalarials, and 74% were taking corticosteroids. Of those taking corticosteroids at initiation of belimumab, the mean daily prednisone equivalent dose was 12.2 mg/day (range 5 to 50 mg/day). The majority of patients (66%) were taking immunosuppressive medications, with 21% taking azathioprine and 34% mycophenolate mofetil. No patients were concurrently receiving cyclophosphamide or rituximab.

Clinical manifestations. The breakdown of clinical manifes-

Table 1. For all patients with SLE: baseline demographics, concomitant medications, and clinical manifestations leading to treatment with belimumab.

Characteristics	Baseline, n = 195
Female (%)	92
Mean age at diagnosis, yrs, range	40.7 ± 13.7 (4 to 65)
Disease duration at initiation of belimumab, yrs, n = 151	11.9 ± 8.1
Age at initiation of belimumab, yrs, range	41.8 ± 12.7 (15 to 73)
Race, %	
White	61
Black	29
Asian	6
Other	2
Ethnicity, %	
Hispanic/Latino	11
Clinical manifestations, %	
Arthritis	67
Rash	44
Constitutional	25
Inability to taper steroids	30
Renal	11
Neuropsychiatric SLE	9
More than 2 manifestations	67
Laboratory manifestations, %	
Hematologic	15
Hypocomplementemia	53
Elevated anti-dsDNA antibodies	37
Concomitant medications, %	
Antimalarials	73
Prednisone	74
Mean dose prednisone equivalent	12.2 mg/day (range: 5 to 50 mg/day)
Immunosuppressive agents	66
Mycophenolate	34
Azathioprine	21
Methotrexate	11
Angiotensin-converting enzyme inhibitor	6
No SLE medications	7

SLE: systemic lupus erythematosus.

tations requiring treatment at the initiation of belimumab is detailed in Table 1. The main clinical manifestations driving treatment were musculoskeletal and mucocutaneous. Proteinuria was present in 11% of patients at the time of initiation of belimumab.

Belimumab was used off-label in 7 patients who were not taking any background SLE medications at the time of initiation, although 4 were taking daily oral corticosteroids. The clinical manifestations resulting in treatment were rash, arthritis, and serositis. One of the 7 patients began taking belimumab for constitutional symptoms.

Fifteen patients were taking only antimalarial treatment at the time of initiation of belimumab. The main clinical manifestations driving treatment were rash, arthritis, and serositis. Four patients had hematological abnormalities, and 2 had constitutional symptoms.

Response to belimumab. At 3 months of belimumab treatment, 52% of patients clinically responded with improvement in the clinical manifestations that led to initiation of belimumab (Figure 1). At 3 months, 61% of patients who started belimumab for arthritis, 43% of patients with rash, and 78% of patients with renal manifestations responded to therapy. At 6 months, data about 120 patients were available for analysis and showed 51% with clinical response. Responders included 46% of patients with arthritis, 52% of patients with rash, and 57% of patients with renal manifestations. The mean daily prednisone equivalent dose of corticosteroids decreased to 9.3 mg/day at 6 months from 12.2 mg/day at baseline [p = not significant (NS)].

At 3 months after initiation of belimumab, 68 of 103 patients (66%) had at least a 25% increase in C3 values, and 35 of 72 patients (51%) had a 25% decrease in anti-dsDNA values (Figure 1). This was maintained at 6 months, with 67% of patients demonstrating at least a 25% decrease in anti-dsDNA values. No significant differences were found in either clinical or laboratory response rates in patients on different background immunosuppressive medications (data not shown).

Elderly patients. Four patients were over 65 years of age at the time of initiation of belimumab therapy, and it was initiated off-label. The clinical manifestations driving treatment were arthritis in all patients and serositis in 2 patients. All patients were taking oral prednisone daily at the time of initiation of therapy, with a range of 3 to 11 mg/day. Only 1 patient was taking another immunosuppressive (mycophenolate mofetil), and no patients were taking hydroxychloroquine. Two patients had elevated levels of anti-dsDNA antibodies, but no patients had hypocomplementemia. At 6 months, only 1 patient responded to therapy with resolution of arthritis and serositis, and all patients continued to take the same baseline dose of prednisone.

Black patients. Data on blacks, although limited, show a similar pattern of improvement. Of 57 black patients, 4 were receiving no background medications at the start of belimumab. There were 17 patients taking corticosteroids. The major clinical manifestations for initiation of belimumab were arthritis, inability to taper steroids, and rash. When compared to the non-black patients in the cohort, black patients showed a higher clinical response rate to belimumab at 3 months (82% vs 45%, p = 0.0001). Data were available for 21 black patients taking belimumab for 6 months; 67% responded to belimumab.

Patients with lupus nephritis. Twelve patients in the cohort had a history of lupus nephritis and proteinuria > 1000 mg/24 h at the time of initiation of belimumab. Followup data were available on 6 of these patients; 3 patients had > 50% improvement in proteinuria after initiation of belimumab.

Childhood-onset SLE. A subset of 39 patients treated with belimumab, most of whom were female, were diagnosed with

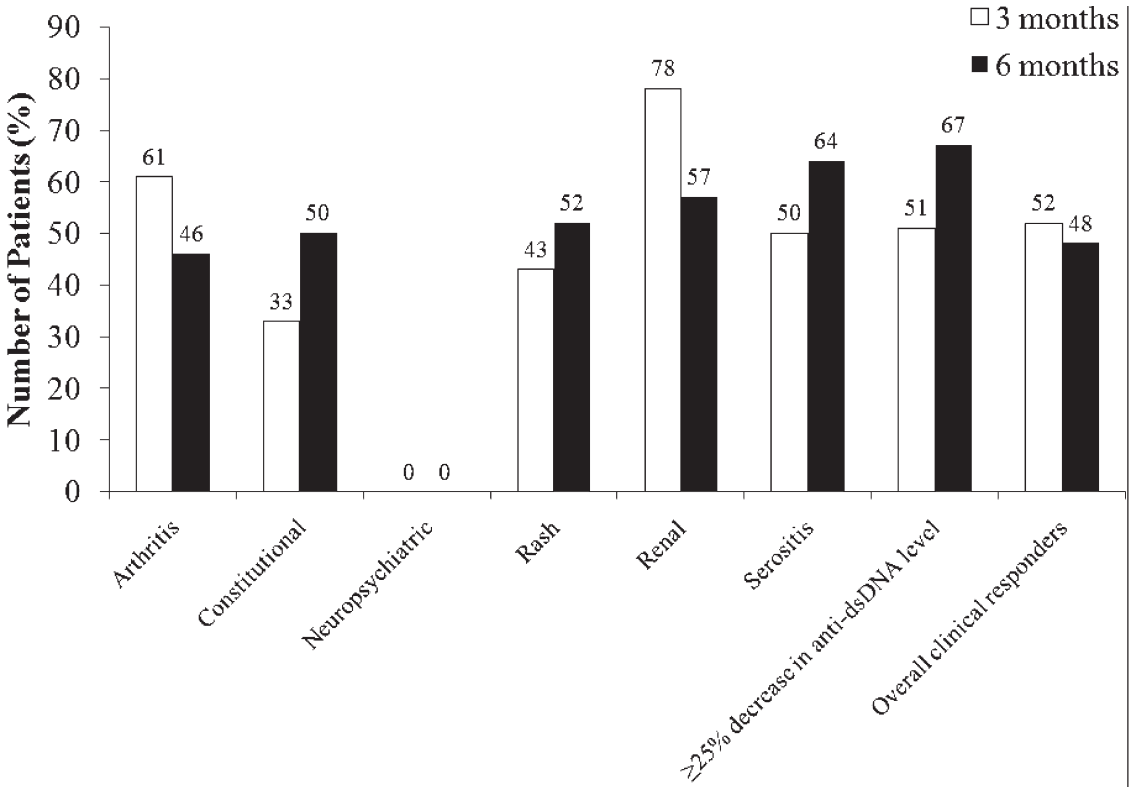

Figure 1. Response to belimumab in all patients with SLE at 3 and 6 months after initiation of belimumab. Data were available on 158 patients at 3 months and 120 patients at 6 months of treatment. Clinical response was defined as the treating physician's impression of ≥ 50% improvement in the initial manifestation(s) being treated and no worsening in other organ systems. Improvement in serology included at least 25% decrease in anti-dsDNA level from baseline. SLE: systemic lupus erythematosus.

SLE prior to their 18th birthday (Table 2), with a mean disease duration of 12 ± 8 years at initiation of belimumab. Four patients were under 18 years of age at the time of initiation of belimumab therapy, and it was initiated off-label. All patients with childhood-onset SLE were taking background medications at the start of belimumab, including 82% who took corticosteroids with a mean daily prednisone equivalent dose of 17 mg, compared to 72% of patients with adult-onset SLE, who took corticosteroids with a mean daily dose of 11 mg ($p < 0.01$). The main clinical manifestations treated in childhood-onset SLE were musculoskeletal and mucocutaneous ones, along with the inability to taper corticosteroids. In the 4 patients under 18 years of age who were treated off-label, the clinical manifestations leading to the decision to treat were rash in 2 patients, thrombocytopenia in 1, and inability to taper steroids in all 4. Clinical improvement was detected as early as 3 months after initiation of therapy in 41% of patients with childhood-onset SLE. At 6 months of treatment with belimumab, 65% of patients with childhood-onset SLE had clinically responded compared to 45% of patients with adult-onset SLE (p = NS; Figure 2). In addition, 18% of patients with childhood-onset SLE who took belimumab had at least a 25% improvement in C3 levels, and 44% had at least a 25% decrease in anti-dsDNA values 3 months after starting belimumab ($p = 0.0001$), and this was maintained at 6 months.

Moreover, 6 months after initiation of belimumab, the mean prednisone equivalent dose decreased from 17 mg/day in those with childhood-onset SLE to 11 mg/day. Steroids were discontinued in 35% of patients with childhood-onset SLE 6 months after belimumab initiation, as compared with 11% of patients with adult-onset SLE ($p = 0.002$).

Safety. Data on adverse events and discontinuation of belimumab are presented in Table 3. No deaths were reported and 32 patients (16%) discontinued belimumab after an average of about 9 months across all sites. The most common adverse effects and reasons for discontinuation were infection and lack of response to belimumab. The most serious infection was Group A streptococcal bacteremia, which occurred in 1 patient. That patient had an elective cervical lymph node biopsy performed 5 days prior to development of bacteremia. The lack of response to belimumab included patients who demonstrated no improvement and/or worsening clinical manifestations of disease, or developed new organ system involvement, as judged by the treating physicians.

Of note, 4 patients developed features of neuropsychiatric SLE (NPSLE) while taking belimumab (1 with stroke, 1 with psychosis, 1 with severe depression, and 1 with new-onset seizures), and 2 patients who had existing NPSLE experienced worsening of disease while taking belimumab (1 with worsening depression, the other without specifics reported).

Table 2. Childhood-onset vs adult-onset patients with SLE: baseline demographics, concomitant medications, and clinical manifestations leading to treatment with belimumab.

Characteristics	Baseline	
	Childhood-onset SLE, n = 39	Adult-onset SLE, n = 156
Women (%)	90	92.3
Mean age at diagnosis, yrs	14 ± 4	33 ± 12
Disease duration at initiation of belimumab, yrs	12 ± 8	11 ± 7
Age at initiation of belimumab, yrs	27 ± 7*	45 ± 11*
Race, %		
White	46	65
Black	48	25
Asian	6	6
Other	0	4
Ethnicity, %		
Hispanic/Latino	12	4
Clinical manifestations, %		
Arthritis	46	70
Rash	36	45
Constitutional	13	27
Inability to taper steroids	82	28
Renal	15	11
Neuropsychiatric SLE	0	10
Laboratory manifestations, %		
Hematologic	5	12
Hypocomplementemia	59	52
Elevated anti-dsDNA antibodies	84	29
Concomitant medications, %		
Antimalarials	92	68
Prednisone	82*	72
Mean dose prednisone equivalent	17 mg/day*	11 mg/day
Immunosuppressive agents	72	53
Mycophenolate	49	33
Azathioprine	23	20
Methotrexate	0	14
Angiotensin-converting enzyme inhibitor	8	4
No SLE medications	0	4

* $p < 0.05$. SLE: systemic lupus erythematosus.

There were also 3 patients who developed or experienced worsening of lupus nephritis over a year after initiation of therapy.

A total of 9 black patients discontinued belimumab: 2 owing to exacerbation of renal disease, 2 for development of or worsening neuropsychiatric disease, 1 because of arthritis flare, and 1 owing to worsening myositis. Discontinuation reasons not related to SLE included 1 infusion reaction, 1 who lost her insurance, and 1 who self-discontinued.

DISCUSSION

Belimumab is the first FDA-approved drug for the treatment of SLE in several decades and marks a breakthrough in drug development in SLE[21]. Our study evaluates the efficacy and safety of belimumab in 10 large academic clinical practices, and is the first report, to our knowledge, of the efficacy and safety of belimumab in childhood-onset SLE.

Posthoc analyses of the phase II belimumab trial data resulted in the development of a novel SLE responder index (SRI), which served as a primary endpoint in the phase III program[22]; however, the stringency of this index precludes its practical use in routine clinical settings. Therefore, the definition of clinical response we used is a simplified version of the SRI; clinical response in our study was constructed around the treating physician's subjective assessment of at least 50% improvement in clinical manifestations, in line with the Systemic Lupus Erythematosus Disease Activity Index SRI-50[23,24]. Our data suggest that clinical improvement in response to belimumab may be detected as early as 3 months after initiation of therapy, and 51% of patients show a response at 6 months. Improvements in complement and dsDNA antibody levels were seen as early as 3 months after initiation of belimumab therapy and continued through the 6-month followup.

Since the results of the phase III trials, postmarketing analyses have consistently demonstrated arthritis and muco-

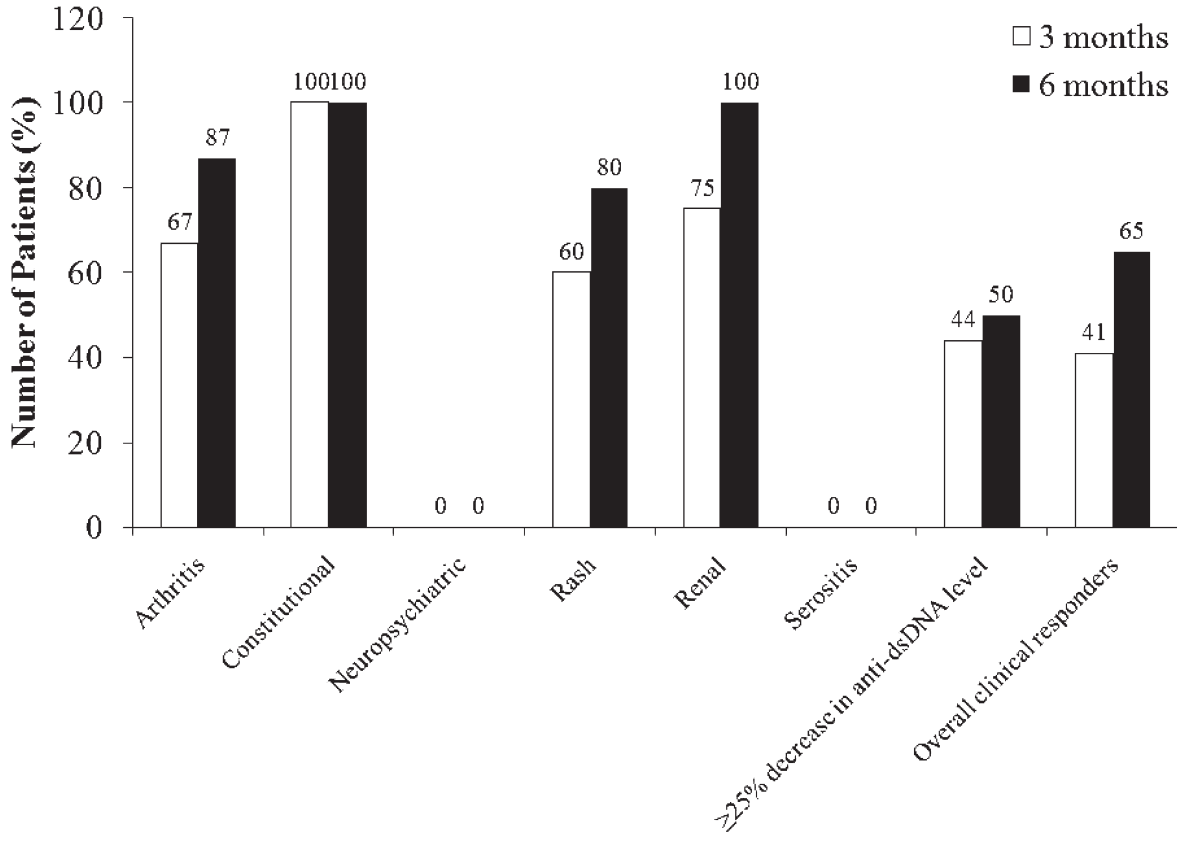

Figure 2. Response to belimumab in patients with childhood-onset SLE at 3 and 6 months after initiation of belimumab. Data were available on 35 patients at 3 months and 26 patients at 6 months of treatment. Clinical response was defined as the treating physician's impression of ≥ 50% improvement in the initial manifestation(s) being treated and no worsening in other organ systems. Improvement in serology included at least 25% decrease in anti-dsDNA level from baseline. SLE: systemic lupus erythematosus.

Table 3. Adverse events and reasons for discontinuation of belimumab.

Reasons for Discontinuation	No. Patients
Development/worsening neuropsychiatric SLE	6
Severe disease flares	4 (renal, arthritis)
Myocardial infarction	1
Loss of insurance	2
Infection	7 (most severe: pneumonia, Group A streptococcal bacteremia, axillary MRSA)
Infusion reaction	3
Elective surgery	1
Patient choice	2
No clinical response	6
Total (out of 195)	32 (16%)

SLE: systemic lupus erythematosus; MRSA: methicillin-resistant *Staphylococcus aureus*.

cutaneous disease as common indications for the initiation of belimumab therapy[25]. Interestingly, < 5% of the cohort as a whole were being treated with methotrexate prior to initiation of belimumab. Our data in a subset of patients with childhood-onset SLE demonstrate similar trends; however, our data also show that over 80% of patients with childhood-onset SLE were given belimumab because of an inability to taper existing steroids for treatment of SLE. Patients with childhood-onset SLE may respond as quickly as 3 months after initiation of belimumab (41%) and a greater proportion responded to belimumab (65%) than did patients with adult-onset SLE (45%) at 6 months (p = NS). The ability to taper and often discontinue corticosteroids in patients with childhood-onset SLE while taking belimumab treatment may, in part, reflect a degree of noncompliance to oral immunosuppressive medications in these patients.

Despite the small sample sizes in our study, serologically positive patients with SLE responded favorably to treatment with belimumab plus standard-of-care therapy. This is consistent with the phase III belimumab trials[7,8,26]. Moreover, given the higher prevalence of SLE in black patients[27,28], it is of interest to note that 67% of a subset of black patients responded to belimumab therapy at 6 months. Subset analyses in phase III trials yielded lower response rates of black patients receiving belimumab versus those receiving placebo. Our data demonstrate a better clinical response rate in blacks that is significantly higher than those of other racial

or ethnic subsets. Thus, results from clinical trials currently under way would be of utmost importance in individually tailoring therapy for black patients.

Further studies in a larger population and for a longer time will also make it possible to examine longterm outcomes and delineate adverse events. Ginzler, *et al*[29] recently noted that there was a reduced risk of SLE flare and continued improvement in clinical and laboratory markers 7 years after initiation of belimumab therapy. Studies in patients with lupus nephritis and/or NPSLE would also help define the role for belimumab and describe the target population for optimal response. Although patients with NPSLE have been excluded from trials to date, there are ongoing trials using belimumab for patients with lupus nephritis that will provide more definitive answers.

Although data are limited, belimumab appears to be well tolerated; 16% of patients experienced an adverse event. This is a much lower rate of occurrence than that reported by Wallace, *et al*[30] in a posthoc analysis of the phase III trials. In the phase III trials, 6% of patients developed depression, and 0.1% had suicidal ideation while taking belimumab therapy. In our cohort, there were 6 patients who developed or had an exacerbation of existing NPSLE; belimumab was discontinued in all those patients. Wallace, *et al*[30] also noted a small percentage of renal disease flare in patients taking belimumab therapy. In addition, Dooley, *et al*[31] demonstrated in a posthoc analysis of the phase III trial patients that of the 267 patients with renal disease at the time of initiation of belimumab therapy, those taking baseline immunosuppressive medications or with serologic activity at baseline had greater renal improvement with belimumab than those with placebo. The effect on renal disease was mixed: Dooley, *et al* noted that both renal flares and reduction of renal symptomatology such as proteinuria and serologic activity appeared to occur more frequently in patients taking belimumab, but the data were not statistically significant when compared with placebo. Our data show that 3 patients developed or had an exacerbation of lupus nephritis; all were patients with childhood-onset SLE. However, in those patients, noncompliance with background standard-of-care SLE immunosuppressive medications may have also played a role in worsening lupus nephritis.

Moreover, given that we defined the lack of response to be no improvement and/or worsening disease in any involved organ system, and/or development of disease in another previously uninvolved organ system, it is possible that the inclusion of these patients in calculating our response rate may reflect a lower rate of response than could be expected. Other limitations include the short time of followup (6 months) in our study, and the lack of comparison to a control group. This may have led us to overstate the efficacy of belimumab in our population.

Our study further substantiates the safety and efficacy of belimumab in the treatment of SLE. The higher clinical response rate among black patients, with comparable safety, is reassuring and should help alleviate concerns regarding the use of belimumab in this racial group. Overall, belimumab appears to be well tolerated; however, caution is advised with its use in patients with SLE who have active NPSLE and/or renal disease until more data are available. Moreover, our data suggest a larger role for belimumab as a corticosteroid-sparing agent in childhood-onset SLE, given that 35% of patients were able to discontinue steroid treatment after the addition of belimumab to standard-of-care SLE treatments. The results of the clinical trials currently under way in pediatric patients with SLE (under 18 years of age) will be of interest in demonstrating the efficacy and safety of belimumab in this population.

ACKNOWLEDGMENT

We thank the patients for their participation in our study.

REFERENCES

1. Askanase A, Shum K, Mitnick H. Systemic lupus erythematosus: an overview. Soc Work Health Care 2012;51:576-86.
2. Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. Nat Rev Rheumatol 2014;10:97-107.
3. Parodis I, Axelsson M, Gunnarsson I. Belimumab for systemic lupus erythematosus: a practice-based view. Lupus 2013;22:372-80.
4. Cancro MP, D'Cruz DP, Khamashta MA. The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. J Clin Invest 2009;119:1066-73.
5. Zhang J, Roschke V, Baker KP, Wang Z, Alarcon GS, Fessler BJ, et al. Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. J Immunol 2001;166:6-10.
6. Petri M, Stohl W, Chatham W, McCune WJ, Chevrier M, Ryel J, et al. Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. Arthritis Rheum 2008;58:2453-9.
7. Navarra SV, Guzman 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.
8. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova 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.
9. Mina R, Brunner HI. Pediatric lupus—are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? Rheum Dis Clin North Am 2010; 36:53-80, vii-viii.
10. Font J, Cervera R, Espinosa G, Pallares L, Ramos-Casals M, Jimenez S, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis 1998;57:456-9.
11. Brunner HI, Gladman DD, Ibanez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum 2008;58:556-62.
12. Hersh AO, von Scheven E, Yazdany J, Panopalis P, Trupin L, Julian L, et al. Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. Arthritis Rheum 2009;61:13-20.

13. Ramírez Gómez LA, Uribe Uribe O, Osio Uribe O, Grisales Romero H, Cardiel MH, Wojdyla D, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. Lupus 2008;17:596-604.
14. Tucker LB, Menon S, Schaller JG, Isenberg DA. Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol 1995;34:866-72.
15. Tucker LB, Uribe AG, Fernandez M, Vila LM, McGwin G, Apte M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). Lupus 2008;17:314-22.
16. Hui-Yuen JS, Imundo LF, Avitabile C, Kahn PJ, Eichenfield AH, Levy DM. Early versus later onset childhood-onset systemic lupus erythematosus: clinical features, treatment and outcome. Lupus 2011;20:952-9.
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
18. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677-86.
19. Petri M, Barr SG, Buyon J, Davis J, Ginzler E, Kalunian K. RIFLE: Responder Index for Lupus Erythematosus [abstract]. Arthritis Rheum Suppl 2000;43 Suppl:S244.
20. Yee CS, Farewell V, Isenberg DA, Griffiths B, Teh LS, Bruce IN, et al. The BILAG-2004 index is sensitive to change for assessment of SLE disease activity. Rheumatology 2009;48:691-5.
21. Mosca M, van Vollenhoven R. New drugs in systemic lupus erythematosus: when to start and when to stop. Clin Exp Rheumatol Suppl 2013;31 Suppl 78:S82-5.
22. Furie RA, Petri MA, Wallace DJ, Ginzler EM, Merrill JT, Stohl W, et al. Novel evidence-based systemic lupus erythematosus responder index. Arthritis Rheum 2009;61:1143-51.
23. Touma Z, Gladman DD, Ibanez D, Urowitz MB. Development and initial validation of the systemic lupus erythematosus disease activity index 2000 responder index 50. J Rheumatol 2011; 38:275-84.
24. Touma Z, Gladman DD, Ibanez D, Taghavi-Zadeh S, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000 Responder Index-50 enhances the ability of SLE Responder Index to identify responders in clinical trials. J Rheumatol 2011; 38:2395-9.
25. Askanase AD, Yazdany J, Molta CT. Post-marketing experiences with belimumab in the treatment of SLE patients. Rheum Dis Clin North Am 2014;40:507-17, viii.
26. van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012;71:1343-9.
27. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Arthritis Rheum 2007;56:2092-4.
28. Pineles D, Valente A, Warren B, Peterson MG, Lehman TJ, Moorthy LN. Worldwide incidence and prevalence of pediatric onset systemic lupus erythematosus. Lupus 2011;20:1187-92.
29. Ginzler EM, Wallace DJ, Merrill JT, Furie RA, Stohl W, Chatham WW, et al. Disease control and safety of belimumab plus standard therapy over 7 years in patients with systemic lupus erythematosus. J Rheumatol 2014;41:300-9.
30. 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.
31. Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A, Roth DA, et al. Effect of belimumab treatment on renal outcomes: results from the phase III belimumab clinical trials in patients with SLE. Lupus 2013;22:63-72.