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Treatment of Lupus Nephritis With Abatacept

The Abatacept and Cyclophosphamide Combination Efficacy and Safety Study

The ACCESS Trial Group

Objective. **To assess the efficacy and safety of a 24-week course of abatacept in the treatment of active lupus nephritis and to assess the potential of abatacept to induce "clinical tolerance," defined as sustained clinical quiescence of lupus nephritis after discontinuation of immunosuppressive therapy.**

Methods. **Patients with active lupus nephritis (n = 134) were enrolled in a randomized, double-blind phase II add-on trial in which they received either abatacept or placebo in conjunction with the Euro-Lupus Nephritis Trial regimen of low-dose cyclophosphamide (CYC) followed by azathioprine (AZA). The primary efficacy outcome was the frequency of complete response at week 24. Thereafter, patients who met either complete or partial response criteria continued blinded treatment through week 52. During this phase of the study, subjects in the abatacept treatment group in whom a complete response was achieved at week 24 discontinued immunosuppressive therapy other than prednisone (10 mg/day).**

Results. **There were no statistically significant differences between groups with respect to the primary outcome or any of the secondary outcomes, including measures of safety. A complete response was achieved in 33% of the subjects in the treatment group and in 31% of the subjects in the control group at week 24. Fifty**

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The principal investigators of the ACCESS Trial, Drs. Wosfy and Diamond, have received consulting fees from Bristol-Myers Squibb in the past but did not receive any remuneration from Bristol-Myers Squibb for the conduct or analysis of this trial. Their participation in this trial was supported in part by their institutions.

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percent of the subjects in the treatment group who met complete response criteria and therefore discontinued immunosuppressive therapy at week 24 maintained their complete response status through week 52.

***Conclusion*. The addition of abatacept to a regimen of CYC followed by AZA did not improve the outcome of lupus nephritis at either 24 or 52 weeks. No worrisome safety signals were encountered.**

There are no consistently safe and effective treatments for lupus nephritis. Induction therapy for active nephritis typically consists of moderate-to-high-dose glucocorticoids combined with an additional potent immunosuppressive drug, followed by maintenance therapy involving long-term sustained immunosuppression (1). Despite this aggressive approach to treatment, many patients continue to have active nephritis and/or recurrent flares, and all patients are exposed to the risks of therapy, including the potential for fatal complications.

For several decades, the standard of care for active lupus nephritis consisted of monthly intravenous pulses of cyclophosphamide (CYC) for at least 6 months, with a target of achieving modest depression of circulating leukocyte counts between doses. This approach had emerged from a relatively small trial that compared high-dose glucocorticoids alone with several alternative regimens consisting of glucocorticoids in combination with other immunosuppressive agents (2). Progression to renal failure occurred most often among patients who received glucocorticoids alone. Although the trial did not distinguish convincingly among the various combination regimens, the community adopted pulse CYC as the preferred approach. In recent years, 2 other approaches have been compared to high-dose pulse CYC and appear to have equivalent efficacy. One approach is based on the Euro-Lupus Nephritis Trial (ELNT). It uses a shorter and less intense regimen of CYC followed by maintenance therapy with azathioprine (AZA) (3,4). The other approach uses mycophenolate mofetil (MMF) instead of pulse CYC (5–8). There is reason to believe that these regimens may be safer than high-dose pulse CYC.

Against this background, there has been great hope that the advent of targeted biologic therapies would lead to breakthroughs in the treatment of lupus nephritis. Thus far, however, these hopes have not been realized (1,9). CTLA-4Ig is among the biologic interventions that have generated great interest. The rationale for testing CTLA-4Ig in lupus nephritis is very strong. CTLA-4Ig blocks binding of antigen-presenting cells to CD28 on T cells, thereby inhibiting activation of primary T cell–dependent immune responses (10). CTLA-4Ig may also have direct inhibitory effects on the B cell lineage, as CD28 is expressed on plasma cells; whether CD28 engagement mediates positive or negative regulation remains a subject of controversy (11–13). In murine models of systemic lupus erythematosus (SLE), CTLA-4Ig acts synergistically with CYC to arrest lupus nephritis (14,15). In humans, CTLA-4Ig (abatacept) is effective in the treatment of rheumatoid arthritis (RA) (16,17). Moreover, a post hoc analysis of a large trial of abatacept in patients with lupus nephritis strongly suggested clinical benefit (18). Finally, a recent study of patients with focal segmental glomerulosclerosis showed that treatment with abatacept induced disease remission, apparently by binding to CD80 on renal podocytes (19). Taken together, these observations provide a strong foundation for postulating that abatacept may be effective in patients with lupus nephritis.

PATIENTS AND METHODS

Study design and treatment protocol. The Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (ACCESS) trial was a 1:1 randomized, double-blind, controlled phase II multicenter trial of abatacept versus placebo on a background of treatment with glucocorticoids plus CYC followed by AZA in patients with active lupus nephritis. The trial consisted of 2 phases. In the first phase, patients with active lupus nephritis were randomized to receive monthly infusions of either placebo or abatacept (supplied by Bristol-Myers Squibb). Subjects in both groups also received 6 biweekly pulses of CYC followed by oral AZA based on the ELNT regimen (3) as well as a tapering regimen of oral glucocorticoids. The primary outcome measure was the proportion of subjects in whom a complete response was achieved at week 24.

Treatment was initiated with monthly infusions of either placebo or abatacept at doses that were adjusted for body weight according to the abatacept dose that is recommended for RA (for $<$60 kg, 500 mg; for 60–100 kg, 750 mg; for $>$100 kg, 1 gm). All patients received 6 intravenous pulses of 500 mg of CYC at 2-week intervals followed by oral AZA at 2 mg/kg/day based on the ELNT regimen. This control regimen differed slightly from the original ELNT regimen with respect to the approach to glucocorticoid treatment. Unlike the ELNT, the ACCESS trial did not use an initial intravenous pulse of glucocorticoids, but rather left that decision to the site investigator's discretion. Oral glucocorticoid treatment was begun at 60 mg/day for 2 weeks in all subjects, followed by a prescribed taper to 10 mg/day over the next 10 weeks.

The second phase of the trial (weeks 24–52) was exploratory and was intended to generate preliminary data regarding the potential of abatacept to restore self-tolerance, defined as sustained quiescence of nephritis in the absence of immunosuppressive therapy. In this phase, patients who met the complete response criteria while receiving abatacept at week 24 then discontinued immunosuppression with abatacept

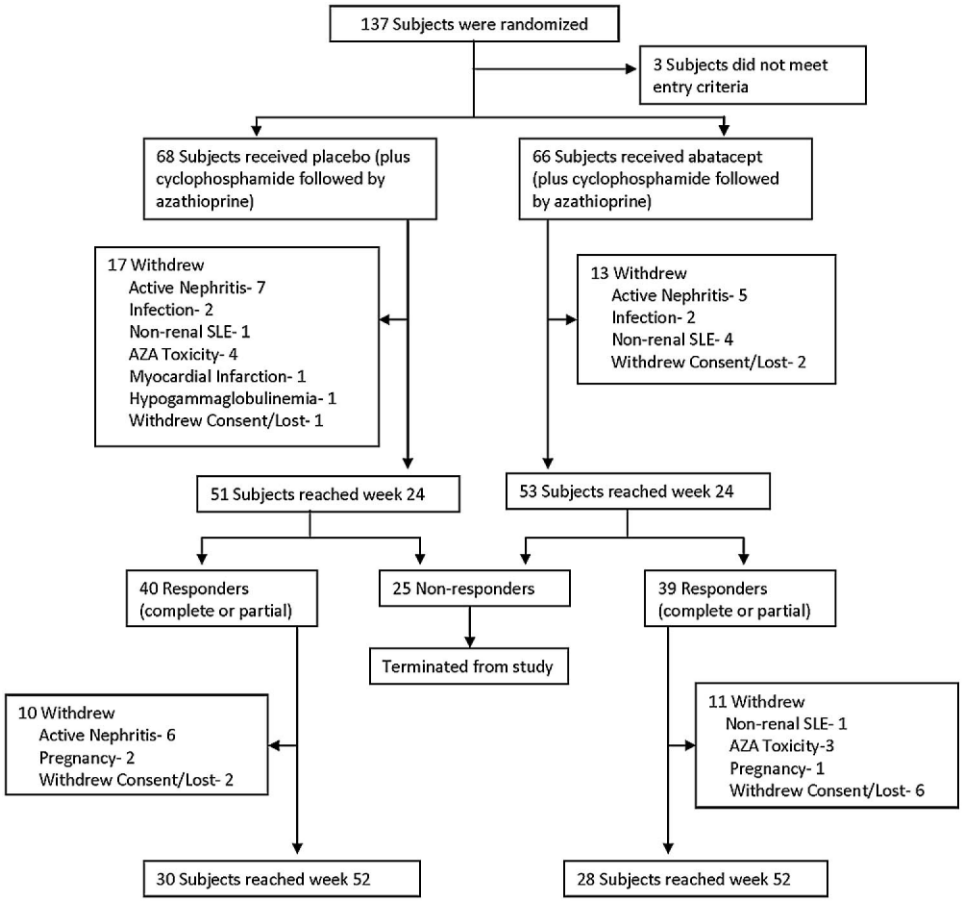

Figure 1. Disposition of the patients in the intent-to-treat population. SLE = systemic lupus erythematosus; AZA = azathioprine.

and AZA at week 28 and continued to take only prednisone 10 mg/day. Patients in whom only a partial response was achieved with abatacept continued therapy with monthly infusions of abatacept and daily oral AZA. In the control group, patients in whom either a complete or partial response was achieved continued to receive AZA. Patients who were nonresponders at week 24 discontinued the trial at that point. Institutional review boards at all sites approved the study design, and all subjects provided written informed consent.

Study subjects. Eligible subjects were 16 years of age or older. They fulfilled the American College of Rheumatology criteria for SLE (20), and they had a positive antinuclear antibody and/or a positive anti–double-stranded DNA (anti-dsDNA) antibody test result at study entry. All subjects had active lupus nephritis, defined by kidney biopsy findings within the last 12 months of proliferative nephritis according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria (21) (class III or class IV, with or without features of class V), and urinary protein-to-creatinine ratio of >1. Overall, 137 subjects were enrolled, of whom 134 met entry criteria and comprised the intent-to-treat population for the efficacy analysis. Study subjects came from 19 sites in the US and 2 sites in Mexico. Enrollment began in November 2008 and concluded in June 2012.

Study end points and assessments. The primary efficacy end point was the proportion of subjects in whom a complete renal response was achieved at week 24. Complete response was defined as *all* of the following: urinary protein-to-creatinine ratio of <0.5 based on a 24-hour urine collection, serum creatinine level of ≤1.2 mg/dl *or* ≤125% of baseline, and adherence to the prednisone taper to 10 mg/day by week 12.

Prospectively defined secondary efficacy end points included the proportion of subjects in whom a partial response was achieved at week 24, defined by the same criteria as the complete response definition except that the urinary protein-to-creatinine ratio component of the partial response definition required only a 50% improvement from baseline rather than a decline to <0.5; the proportion of subjects who met the urinary protein-to-creatinine ratio and glucocorticoid criteria for complete response at week 24; the proportion of subjects who met the urinary protein-to-creatinine ratio and glucocorticoid criteria for partial response at week 24; the proportion of subjects who met either complete response or partial response

criteria at week 52; the proportion of subjects in whom a complete response was achieved at week 24 and in whom that response was maintained to week 52; time to complete response or partial response; and lupus disease activity as reflected by reduction in anti-dsDNA antibody levels, resolution of hypocomplementemia (C3 or C4), patient's global assessment, the Short Form 36 (SF-36) health survey score (22), and the British Isles Lupus Assessment Group (BILAG) 2004 score (23).

Secondary efficacy end points also included the frequency of lupus flares, either renal or nonrenal. For subjects in whom a complete response had been achieved at week 12 or any time thereafter, a renal flare was defined as the recurrence of proteinuria of >1 gm/24 hours. For all others, a renal flare was defined as either of the following: serum creatinine level at least 25% higher than baseline or above the upper limit of normal, plus proteinuria at least 75% of baseline; or doubling of the urinary protein-to-creatinine ratio compared with the lowest previous value. A nonrenal flare was defined by the BILAG 2004 guidelines as any new "A" finding in a nonrenal organ system. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Power and sample size. Using data from the ELNT (3,4), the statistical analysis plan was based on the assumption that the proportion of complete response outcomes at week 24 in the control group would be 20%. Our goal was to detect a 30% increase in the complete response rate in the abatacept group (50% compared to 20%). Subjects who dropped out of the study prior to week 24 were considered to be clinical response failures for the primary analysis. As such, after adjusting for an expected 10% dropout rate equally distributed between the 2 groups, this difference corresponds to an expectation of 45% complete response in the abatacept group and 18% complete response in the control group. To detect this 27% difference at 90% power using a 2-sided Fisher's exact test at the 0.05 level of significance, a sample size of 67 subjects per group was required.

RESULTS

Study population. Sixty-eight subjects were randomized to the control group, and 66 subjects were randomized to the abatacept treatment group (Figure 1). Baseline characteristics were well-matched between treatment groups (Table 1). Approximately 90% of the subjects were women. The mean age at study entry was 32 years. The study population was racially and ethnically diverse; 39% of the subjects were African American and 40% were Hispanic or Mestizo. Thirty-four percent of the subjects had ISN/RPS lupus nephritis class III with or without features of class V, and 66% had class IV with or without features of class V. Forty-six percent of the subjects in the control group and 41% of the subjects in the treatment group entered the trial with a urinary protein-to-creatinine ratio of >3. Seventy-one percent of the subjects in each group had a disease duration of nephritis of <1 year. At the time of study entry, 60% of the subjects were receiving an antimalarial drug, and 73% of the subjects were receiving either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. The use of these agents was comparable between the 2 treatment groups.

Table 1. Patient demographics and baseline characteristics*

Variable	Control (n = 68)	Abatacept (n = 66)
Age, mean ± SD years	32.7 ± 12.0	32.0 ± 10.1
Female	64 (94)	58 (88)
Primary race		
White	33 (49)	34 (51)
African American	25 (37)	27 (41)
Asian	3 (4)	3 (5)
Mixed or undeclared	7 (10)	2 (3)
Ethnicity		
Hispanic/Mestizo	28 (41)	25 (38)
Weight, mean ± SD kg	75 ± 23	74 ± 18
Blood pressure, mean ± SD mm Hg		
Systolic	133 ± 17	130 ± 17
Diastolic	83 ± 11	79 ± 12
Time from onset of lupus nephritis		
<1 year	48 (71)	47 (71)
ISN/RPS classification, no.†		
Class III	11	10
Class IV	24	24
Segmental	8	10
Global	16	14
Class III + V	12	12
Class IV + V	20	20
Renal function, mean ± SD		
Serum creatinine, mg/dl	1.3 ± 0.6	1.2 ± 0.7
Estimated GFR, ml/minute/1.73 m^2	58 ± 28	65 ± 36
Urinary protein		
24-hour total, mean ± SD gm/day	4.5 ± 4.0	3.8 ± 3.1
Protein-to-creatinine ratio, mean ± SD mg/mg	4.1 ± 3.4	3.6 ± 2.6
Urinary protein-to-creatinine ratio >3	31 (46)	27 (41)
Serum albumin, mean ± SD gm/dl	2.7 ± 0.7	2.8 ± 0.6
Serologic features (at randomization)		
ANA positive (≥1:80)	68 (100)	66 (100)
Anti-dsDNA positive	50 (75)	49 (75)
Low C3 complement	44 (70)	47 (78)
Low C4 complement	37 (59)	39 (65)
Patient's global assessment, mean ± SD	45 ± 28	42 ± 30
SF-36, mean ± SD		
Physical component score	39 ± 10	39 ± 11
Mental component score	40 ± 13	40 ± 13

* Except where indicated otherwise, values are the number (%). Percentages are calculated based on the number of subjects with evaluable data. ISN/RPS = International Society of Nephrology/Renal Pathology Society; GFR = glomerular filtration rate; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; SF-36 = Short Form 36 health survey.
† Biopsies were read and classified by pathologists at the local sites.

Primary outcome measure. There was no significant difference in the complete response rate at week 24

between the abatacept and control groups, as determined by Fisher's exact test (Figure 2A). Complete responses occurred in 21 (31%) of 68 control subjects and 22 (33%) of 66 abatacept-treated subjects.

Secondary efficacy outcome measures. The frequency of total responses (complete or partial) was identical in the 2 groups at 59% (Figure 2B). There also were no statistically significant differences in any of the other prespecified secondary outcome measures (Table 2), including the proportion of subjects who met the proteinuria and prednisone requirements for complete response or partial response; the proportion of subjects who had a 75% reduction in anti-dsDNA antibody levels; the proportion of subjects who were negative for anti-dsDNA antibodies; resolution of hypocomplementemia as measured by C3 or C4 levels; time to complete response or partial response; patient's global assessment; SF-36 physical and mental scores; BILAG 2004 score; or the frequency of flares. The mean urinary protein-to-creatinine ratio at week 24 was 1.1 ± 1.2 in the control group compared to 1.1 ± 1.3 in the abatacept group. The complete response rate was lowest among African American subjects in the control group (16% versus 40% among non–African American control subjects), but no such difference was observed in the abatacept group (complete response was achieved in 33% of both the African American and the non–African American subjects), nor were any of the differences among racial and ethnic groups statistically significant. Complete response and partial response rates were not significantly different when comparing subjects with recent onset of nephritis (<1 year) to subjects with a longer history of nephritis (≥1 year) (data not shown).

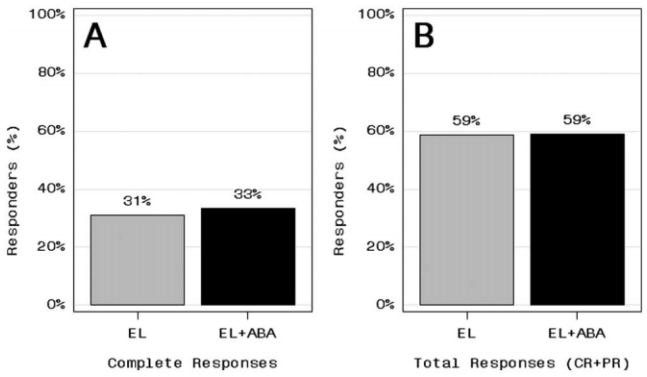

Figure 2. Complete response (CR) rate (**A**) and total response rate (complete responses plus partial responses [PR]) (**B**) at week 24 among control subjects treated with either the Euro-Lupus (EL) Nephritis Trial regimen or the Euro-Lupus Nephritis Trial regimen plus abatacpet (EL + ABA).

Table 2. Secondary outcome measures at week 24*

Outcome measure	Control	Abatacept
Urinary protein-to-creatinine ratio, mean ± SD	1.1 ± 1.2	1.1 ± 1.3
Disappearance of anti-dsDNA antibody	4/36 (11)	9/38 (24)
Correction of low C3 concentration	11/30 (37)	14/38 (37)
Correction of low C4 concentration	10/25 (40)	17/32 (53)
Total BILAG score, mean ± SD	3.4 ± 1.8	3.8 ± 3.0
Patient's global assessment, mean ± SD	28 ± 25	18 ± 22
SF-36, mean ± SD		
Physical component score	45.3 ± 11	45.3 ± 11
Mental component score	46.5 ± 11	45.9 ± 12
Subjects with lupus flares		
Renal flare	3/68 (4.4)	3/66 (4.5)
Nonrenal flare	6/68 (9)	8/66 (12)
Complete response by race/ethnicity		
Race		
White	14/33 (42)	12/34 (35)
African American	4/25 (16)	9/27 (33)
Asian	1/3 (33)	1/3 (33)
Mixed or undeclared	2/7 (29)	0/2 (0)
Ethnicity		
Hispanic/Mestizo	10/28 (36)	8/25 (32)
Not Hispanic/Mestizo	11/40 (28)	14/41 (34)
Total response by race/ethnicity†		
Race		
White	21/33 (64)	22/34 (65)
African American	14/25 (56)	15/27 (56)
Asian	2/3 (67)	1/3 (33)
Mixed race or undeclared	3/7 (43)	1/2 (50)
Ethnicity		
Hispanic/Mestizo	16/28 (57)	15/25 (60)
Not Hispanic/Mestizo	24/40 (60)	24/41 (59)

* Except where indicated otherwise, values are the number of patients/number evaluated (%). Values for urinary protein-to-creatinine ratio were compared using a 2-sided *t*-test from an analysis of covariance (ANCOVA) model on log(urinary protein-to-creatinine ratio) that was adjusted for log(baseline values). Values for disappearance of anti–double-stranded DNA (anti-dsDNA) antibody and lupus flares were compared using a 2-sided Pearson's chi-square test. Values for total British Isles Lupus Assessment Group (BILAG) score were compared using a 2-sided *t*-test from an analysis of variance model. Values for patient's global assessment and Short Form 36 (SF-36) were compared using actual values between experimental and control groups and a 2-sided *t*-test from an ANCOVA model that adjusts for baseline values. None of the differences were statistically significant.

† Total response included patients in whom a complete response or a partial response was achieved.

Safety. There were no clinically or statistically significant differences between the 2 groups at week 24 in total AEs, lupus-related AEs, serious AEs, serious infectious AEs, opportunistic infections, or withdrawals due to AEs (Table 3). There was one death, which was due to sepsis, in the control group.

Outcomes at week 52. Forty subjects from the control group and 39 subjects from the abatacept group continued in the study per protocol beyond the primary

end point at week 24. Their outcomes are shown in Table 4. According to the protocol, the 22 subjects in the abatacept group who met complete response criteria at week 24 discontinued abatacept and AZA at week 28 and continued to take only prednisone 10 mg/day thereafter. Complete response status was maintained in 11 of these subjects (50%) through week 52, compared to 13 (62%) of 21 subjects in the control group in whom complete response status was maintained while continuing AZA through week 52 (*P* not significant). In 1 subject in each group, the status deteriorated from complete response at week 24 to partial response at week 52. Two subjects in the abatacept group and 4 subjects in the control group either withdrew due to a renal flare or failed to meet either complete response or partial response criteria at week 52. One patient in the abatacept group withdrew due to a nonrenal flare, and several subjects in each group withdrew for reasons unrelated to lupus or study treatment. Overall, 13 subjects in the control group withdrew from the trial due to active nephritis, compared to 5 subjects in the abatacept group (Figure 1).

All subjects who were classified as partial responders at week 24 continued to receive immunosuppressive treatment during weeks 24–52. Again, there were no significant differences between groups. The most common outcome in both groups was an improvement from partial response status at week 24 to complete response status at week 52 (Table 4).

There were no statistically significant differences in any of the secondary outcome measures at week 52 (data not shown). With regard to safety between weeks 24 and 52, there were 10 serious AEs (5 in each group), no discontinuations due to infection, and no deaths.

Table 3. Proportion of subjects with AEs through week 24*

	Control (n = 68)	Abatacept (n = 66)
Any AE	56 (82)	56 (85)
Infection-related AEs	32 (47)	31 (47)
Grade 3 or higher AEs	24 (35)	21 (32)
Infection-related grade 3 or higher AEs	5 (7)	8 (12)
Serious AEs	20 (29)	19 (28)
Deaths	1	0
AEs resulting in withdrawal from study	17 (25)	11 (16)

* Values are the number (%). AE = adverse event.

Table 4. Outcome at week 52*

	Control	Abatacept
Patients with a complete response at week 24		
No. of patients	21	22
Status at week 52		
Complete response, no. (%)	13 (62)	11 (50)
Partial response	1	1
Loss of renal response†	4	2
Withdrew (nonrenal SLE flare)	0	1
Withdrew (unrelated to SLE or abatacept)	3	7
Patients with a partial response at week 24		
No. of patients	19	17
Status at week 52		
Complete response, no. (%)	9 (47)	7 (41)
Partial response	4	6
Loss of renal response†	5	1
Withdrew (nonrenal SLE flare)	0	0
Withdrew (unrelated to SLE or abatacept)	1	3
Total response at week 52, no./no. evaluated (%)‡	27/40 (68)	25/39 (64)

* Except where indicated otherwise, values are the number of patients. SLE = systemic lupus erythematosus.
† Either withdrew due to renal flare or did not meet complete response or partial response criteria at week 52.
‡ Total response included patients in whom a complete response was achieved and patients in whom a partial response was achieved.

DISCUSSION

This trial did not demonstrate any benefit of abatacept when added to a regimen consisting of low-dose pulse CYC followed by AZA in patients with lupus nephritis. This finding suggests that abatacept may not be effective in lupus nephritis. However, there are alternative explanations that might account for the outcome. This trial explored only one dose regimen, which was based on the dose of abatacept that is approved for the treatment of RA. It is possible, therefore, that a higher dose might be required for lupus nephritis. Background therapy may be important. In this trial, we chose to use CYC as the foundation for the background regimen, based on studies in murine lupus suggesting potential synergy between abatacept and CYC (14,15). By using a low-dose approach to CYC therapy, we may have used too little to achieve a synergistic benefit. A post hoc analysis of a prior trial of abatacept in lupus nephritis suggested possible benefit on a background of MMF (18), so perhaps a combination with MMF would be more effective. Finally, this add-on trial demonstrated that abatacept does not provide additional benefit when superimposed on background therapy initiated

with high-dose glucocorticoids followed by CYC and AZA. However, it does not establish whether abatacept might demonstrate comparable efficacy in a head-to-head trial design. In that context, it is even possible that the background glucocorticoid therapy or the multiple doses of CYC in this trial interfered with the mechanism of action of abatacept. It may be noteworthy in that respect that the preclinical mouse studies that contributed to the foundation for this trial did not use glucocorticoids at all. Although the alternative explanations for the trial results are all plausible, it would be a daunting task to put them to the test.

A unique aspect of this trial was the opportunity it provided to acquire preliminary data on the impact of discontinuing immunosuppressive therapy in patients in whom a complete response is achieved within 24 weeks. This opportunity resulted from 3 factors. First, there is a biologic rationale for postulating that CTLA-4Ig might induce tolerance among autoreactive T cells (10,24). Second, studies in mice indicate that the beneficial effect of CTLA-4Ig on murine lupus nephritis persists even after treatment is discontinued (25). Third, this trial was supported by the Immune Tolerance Network, which has a mission to evaluate therapies that have the potential to induce clinical tolerance, defined as quiescence of autoimmune disease in the absence of ongoing immunosuppressive therapy. This goal is particularly important in lupus, where it is unknown whether the risks of long-term immunosuppression exceed the risks of discontinuing therapy in patients in whom a complete response is achieved.

There is little information in the literature to address this issue. One trial demonstrated that continued immunosuppression with pulse methylprednisolone plus CYC was preferable to reliance on pulse methylprednisolone alone as maintenance therapy, but that result was based on an examination of the overall study population and did not focus on the minority of subjects in whom complete responses had been achieved (26). Similarly, retrospective analyses of longitudinal cohorts have demonstrated the benefit of maintenance therapy for the entire cohort, but have not provided data about the risk/benefit ratio specifically for subjects without evidence of active disease (27). A recent report described successful withdrawal of immunosuppressive therapy from lupus nephritis patients whose disease was in remission, but in that study the duration of treatment for lupus nephritis varied between 2.5 and 10 years prior to gradual tapering and eventual discontinuation of therapy (28).

In the ACCESS trial, we discontinued immunosuppressive therapy in 22 subjects in the abatacept treatment group who met complete response criteria at week 24, because those were the subjects in whom the scientific rationale for discontinuing therapy was strongest. Complete response status was maintained in 11 of those subjects through week 52. The 50% success rate at maintaining complete response in this group was similar to the 62% success rate among subjects in the control group (13 of 21) who continued to receive AZA and met complete response criteria at week 24. These exploratory findings cannot be interpreted to imply that abatacept contributed to the sustained quiescence, but they raise the possibility that, once a complete response is achieved, it may be possible to discontinue immunosuppression, monitor patients closely, and avoid the risks of ongoing immunosuppression. There was no difference between the groups in the number of subjects who lost their renal response or had a nonrenal flare between weeks 24 and 52 (3 of 22 complete responders who discontinued immunosuppressive therapy compared to 4 of 21 complete responders who continued AZA maintenance therapy). The number of subjects in this exploratory analysis was small, but the results suggest that further study is warranted to determine whether maintenance therapy should be continued after the establishment of complete response.

The ACCESS trial provided an important opportunity to explore the effectiveness of the ELNT treatment strategy in a racially and ethnically diverse North American population. Previous studies of this regimen strongly suggested that a less aggressive approach to pulse CYC might be as effective as, and safer than, the more intense CYC regimen that has long been the standard of care (3,4). However, those studies involved primarily Northern European lupus patients, of whom most were white patients with new-onset, rather than refractory, nephritis. Due to the nature of the study population, there has been a reluctance to generalize those results to other populations, especially African American and Hispanic populations, who tend to have more severe and refractory disease (29–34). By succeeding in recruiting a racially and ethnically diverse population of lupus patients that more closely resembles the overall demographics of lupus, we have been able to show that the response rates for the ELNT regimen in this population closely match, or slightly exceed, the response rates for high-dose CYC or MMF reported from other trials (6,9), although the efficacy of this regimen in African American subjects warrants further study.

There have now been 2 trials of abatacept in patients with lupus nephritis. Neither trial achieved its primary outcome goal. The prior trial used a control regimen of MMF rather than CYC and AZA (18). Although that trial failed to meet its primary end point, a post hoc analysis suggested that there may have been efficacy that was not captured by the prospectively defined end point (18). Therefore, a second large, multicenter international trial of abatacept on a background of MMF is currently under way (ClinicalTrials.gov identifier: NCT01714817). The results of that trial will provide additional data by which to determine whether abatacept will play a role in the treatment of lupus nephritis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Wofsy and Diamond had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Daikh, Wofsy, Davidson, Diamond, Ding, Gao, Ramos-Remus, Sayre, Tosta, Utset.

Acquisition of data. Askanase, Cagnoli, McCune, Chatham, Dall'Era, Wofsy, Diamond, Mackay, Ding, Gao, Dooley, Fragoso-Loyo, Sanchez-Guerrero, Karp, Olsen, Jolly, Kalunian, Kamen, Lee, Levesque, Lim, Ramos-Remus, Rovin, Utset, Venuturupalli, Winchester.

Analysis and interpretation of data. Byron, Keyes-Elstein, McCune, Contreras, Dall'Era, Wofsy, Diamond, Ding, Gao, Dooley, Ramos-Remus, Sayre, Smilek, Tosta, Utset.

ADDITIONAL DISCLOSURES

Authors Byron and Keyes-Elstein are employees of Rho Inc. Author Levesque is currently employed by AbbVie.

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