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Nonrenal Disease Activity Following Mycophenolate Mofetil or Intravenous Cyclophosphamide as Induction Treatment for Lupus Nephritis

Findings in a Multicenter, Prospective, Randomized, Open-Label, Parallel-Group Clinical Trial

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Objective. **To assess the effect of mycophenolate mofetil compared with intravenous pulses of cyclophosphamide on the nonrenal manifestations of lupus nephritis.**

Methods. **Patients with active lupus nephritis (renal biopsy class III, IV, or V) were recruited for the study (n = 370) and treated with mycophenolate mofetil (target dosage 3 gm/day) or intravenous cyclophosphamide (0.5–1.0 gm/m^2/month), plus tapered prednisone, for 24 weeks. Nonrenal outcomes were determined using measures of whole body disease activity, including the British Isles Lupus Assessment Group (BILAG) disease activity index, the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and immunologic variables.**

Results. **Both treatments were effective on whole body disease activity in the systems examined, as indicated by changes in the classic BILAG index. With either treatment, remission was induced, notably in the mucocutaneous, musculoskeletal, cardiovascular/respiratory, and vasculitis systems, and flares were rare, as measured by the SELENA–SLEDAI. Levels of complement C3, C4, and CH50 and titers of anti–double-stranded DNA antibodies were normalized after treatment with either mycophenolate mofetil or intravenous cyclophosphamide.**

Conclusion. **In addition to the efficacy of both treatments on the renal system, this analysis showed that remission could also be induced in other systems. There was no clear difference in efficacy between mycophenolate mofetil and intravenous cyclophosphamide in ameliorating either the renal or nonrenal manifestations. Mycophenolate mofetil is, therefore, a suitable alternative to cyclophosphamide for the treatment of renal and nonrenal disease manifestations in patients with biopsy-proven lupus nephritis.**

Systemic lupus erythematosus (SLE) is a multisystem disease with the potential to cause pathologic activity and symptoms in every organ system in the body.

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Its most common life-threatening manifestation is autoimmune glomerulonephritis. However, the presentation of SLE varies widely, and therefore individual patients differ substantially with regard to their clinical and serologic manifestations. The disease has a relapsing–remitting course, and relapses and flares affect all systems, not necessarily at the same time. Consequently, it is important to control disease activity throughout the body, including both renal and nonrenal signs and symptoms, to prevent relapse and enhance the patient's quality of life.

Controlled clinical trials in patients with SLE have focused primarily on lupus nephritis, but generally have not analyzed nonrenal manifestations (1,2). Available data are mostly from a study comparing the effects of clofazimine and chloroquine on dermatologic manifestations (3), from a small case series of patients treated with rituximab (4), from a short randomized, placebo-controlled trial of testosterone patches in mild/moderate SLE (5), and from one open-label, double-blind study comparing azathioprine and cyclosporine as steroid-sparing agents in severe SLE (6). A double-blind trial investigating the steroid-sparing effects of methotrexate, compared with placebo, in patients with SLE showed that methotrexate conferred a notable advantage in patients with moderately active lupus, by allowing the daily prednisone dose to be lowered and by slightly decreasing the disease activity (7). One double-blind pilot study demonstrated that leflunomide was more effective than placebo in treating SLE patients with mild-to-moderate disease activity, and the treatment was well tolerated (8). Two further studies showed that leflunomide in combination with prednisone was effective as induction therapy for lupus nephritis, and this regimen was also well tolerated (9,10).

Seven randomized controlled trials have provided evidence that dehydroepiandrosterone (DHEA) has a modest but clinically significant impact on health-related quality of life in the short term in SLE. However, the impact on disease activity was inconsistent, with DHEA showing no benefit over placebo, in terms of change in the SLE Disease Activity Index (SLEDAI), in all but 1 of the 6 studies evaluating this outcome (11). A recent large, double-blind, phase II trial of a monoclonal antibody to B lymphocyte stimulator concentrated on assessing its effects on nonrenal manifestations of lupus. The prospective, blinded phase of that study showed no difference between the treatment and control groups, although subsequent post hoc and open-label followup analyses (12) have suggested possible beneficial effects on disease activity (13,14).

To date, there have been no robust trials assessing the nonrenal effects of mycophenolate mofetil; however, potential nonrenal benefits have been suggested on the basis of observational data. A systematic review of mycophenolate mofetil for nonrenal manifestations of SLE identified 20 relevant articles published between 2000 and 2006 (15). These were all case series or open-label trials, but the limited evidence suggested that mycophenolate mofetil was effective for refractory hematologic and dermatologic manifestations of SLE (15). A retrospective review of the records of 93 patients with SLE found that mycophenolate mofetil was associated with a clinically significant reduction in steroid dosage, European Consensus Lupus Activity Measure score, erythrocyte sedimentation rate, and anti–double-stranded DNA (anti-dsDNA) antibody titer, with an increase in complement C3 levels (16). Therefore, the potential nonrenal benefits of mycophenolate mofetil warrant further study.

Concerns have been raised about the poor quality of clinical trial design and data reporting for trials involving patients with SLE (17). A literature review conducted by the European League Against Rheumatism task force on SLE revealed that most outcome measures used in phase II/phase III trials in SLE have not been validated. Therefore, recommendations for points to consider for conducting clinical trials in SLE were made in the areas of study design, eligibility criteria, and outcome measures (adverse events, concomitant therapies for SLE and its complications) (17), and it is hoped that the Aspreva Lupus Management Study (ALMS) may be able to provide valuable insights for the future design of clinical trials in patients with SLE.

The ALMS has yielded the most extensive global data set thus far to address variations in response to and tolerability of 2 of the most widely used treatments for lupus nephritis, mycophenolate mofetil and intravenous cyclophosphamide. The study has provided an important opportunity to assess the impact of these treatments on a broad range of SLE manifestations. The trial assessed specific nonrenal features of SLE using the British Isles Lupus Assessment Group (BILAG) disease activity index (18,19) as a secondary end point, which provided the opportunity to explore any variation in response to these treatments throughout the different body systems.

This report describes the effect of mycophenolate mofetil and intravenous cyclophosphamide on whole body disease activity following the induction treatment of patients with active lupus nephritis (renal biopsy class III, IV, or V). The objective of these analyses was to determine whether treatment with mycophenolate mofetil or cyclophosphamide induces a response and

prevents flares throughout the body in this patient population.

PATIENTS AND METHODS

Study design. The ALMS trial (protocol WX17801, NIH registration number NCT00377637) was designed as a multicenter, prospective, randomized, open-label, parallel-group clinical trial, the methodology of which has been described in detail elsewhere (20,21) and will be recounted briefly here. Patients (n = 370; ages 12–75 years) with a diagnosis of SLE (by the American College of Rheumatology [ACR] criteria [22]) and lupus nephritis (International Society of Nephrology/Renal Pathology Society classification of active or active/chronic lupus nephritis in renal biopsy class III, class IV-S or IV-G, class V, class III + V, or class IV + V [23]) were recruited. The main exclusion criteria included having received continuous dialysis for more than 2 weeks before randomization, and having an anticipated dialysis duration of longer than 8 weeks. Pulse intravenous corticosteroids were prohibited within 2 weeks prior to the first randomization and throughout the study. During the study, any drugs affecting the angiotensin system were administered at a stable dose.

Patients were randomly assigned to open-label treatment with oral mycophenolate mofetil (titrated from a dosage of 0.5 gm twice daily in week 1 and 1.0 gm twice daily in week 2, to a target dosage of 3 gm/day in week 3) or intravenous cyclophosphamide (monthly pulses of 0.5–1.0 gm/m^2 [24]) for the 24-week induction phase, with safety and efficacy assessments at weeks 2 and 4, followed by treatment every 4 weeks. Both groups also received oral prednisone, with a predefined taper from a maximum starting dosage of 60 mg/day, which was decreased by 10 mg/day every 2 weeks until a dosage of 40 mg/day was reached, and then decreased by a further 5 mg/day every 2 weeks until a dosage of 10 mg/day was reached (20). Reductions below 10 mg/day were allowed after 4 weeks of stable response (20).

Outcome measurements. The primary end point assessed in the ALMS was the proportion of patients responding to treatment, as demonstrated by a decrease in the urinary protein:creatinine ratio and stabilization or improvement in the serum creatinine level at 24 weeks, as adjudicated in a blinded manner by a committee responsible for assessing the clinical end points. For this assessment, 24-hour urine samples were obtained from all patients at baseline and every 4 weeks thereafter, until completion of the 24-week induction phase. Any patient who did not complete the induction phase for any reason or who received pulse methylprednisolone therapy for a major renal or extrarenal flare was classified as a nonresponder; these data, as well as other secondary renal end points, and the safety data have been reported elsewhere (21).

The present study explored the nonrenal findings of the ALMS. The objective was to determine whether mycophenolate mofetil or intravenous cyclophosphamide induces a response and prevents flares in each of the organs/systems assessed by the BILAG index. The end points assessed were measures of whole body disease activity and immunologic parameters. For those patients who completed the study, data are reported through week 24. In contrast, for those patients who exited the study prior to week 24, the end point comprised data from the last value recorded while on treatment (last observation carried forward [LOCF]).

Patients were assessed using the BILAG index of lupus disease activity every 4 weeks, from baseline to 24 weeks. The classic BILAG index (18,19) is a comprehensive clinical index, comprising 86 items for recording lupus disease activity, that is valid, reliable, and sensitive to change (18,25,26). It is a transitional index that can capture the changing severity of clinical manifestations and was developed on the principle of the physician's intent-to-treat (ITT). It has an ordinal-scale scoring system that produces an overview of disease activity across 8 systems: general, mucocutaneous, central nervous system, musculoskeletal, renal, cardiovascular/respiratory, vasculitis, and hematologic. Disease activity is categorized into 5 levels, from grade A to grade E. Grade A represents very active disease, usually considered to require treatment with prednisone dosages of more than 20 mg daily (or equivalent) and/or new or increased doses of other immunosuppressive/cytotoxic drugs. Grade B represents moderate disease activity, requiring lower doses of corticosteroids, antimalarials, or nonsteroidal antiinflammatory drugs. Grade C indicates mild disease, requiring only therapy targeted to specific symptoms, whereas grade D indicates no current disease activity but with a previously affected system (defined as remission). Finally, grade E indicates no current or no previous disease activity in that system (18,19). For patients with active disease, a change in score from grade A or grade B to grade C is a clinically significant response, even if full remission in that system has not been achieved.

Disease activity was assessed using the classic BILAG index (19), with the exception that the renal system was scored using the initial version of the BILAG 2004 index (27,28), because this latter version includes the use of the protein:creatinine ratio and the estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula. Investigators attended a training session for the BILAG scoring system prior to its application in the assessment of disease activity in this cohort.

Disease activity was also assessed using the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the SLEDAI, which is a measure of current disease activity within the 10 days preceding baseline, and includes a definition of flare (29). It is a sum of 24 criteria for 9 organ systems that categorizes high disease activity (score >6), low disease activity (score >2 to ≤ 6), and normal (score ≤ 2). A mild/moderate flare is defined as an increase in the SELENA–SLEDAI score of ≥ 3 (total score <12). A severe flare is defined as an increase in the SELENA–SLEDAI score to ≥ 12 over baseline. To separate the nonrenal from the renal data, the SELENA–SLEDAI scores were calculated with exclusion of the following renal parameters: urinary casts, hematuria, proteinuria, and pyuria. Disease activity determined on the SELENA–SLEDAI was measured at baseline, week 12, week 24, and at the end point.

Accumulated organ/system damage that had occurred since the onset of SLE was assessed using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (30,31) total score at baseline and at the end of the induction period (week 24 or end point). Twelve organs were assessed, with a variable number of components (up to 6) in each, and summed to a maximum of 46 points. At diagnosis, the SDI score is considered to be 0, and higher scores are a predictor of increased mortality. The difference in mean changes in the SDI score between treatment groups was calculated.

Table 1. Demographics and baseline disease characteristics of the patients treated with MMF or IVC*

	MMF (n = 185)	IVC (n = 185)	Total (n = 370)
Sex			
Male	28 (15.1)	29 (15.7)	57 (15.4)
Female	157 (84.9)	156 (84.3)	313 (84.6)
Race			
Caucasian	75 (40.5)	72 (38.9)	147 (39.7)
Asian	62 (33.5)	61 (33.0)	123 (33.2)
Other†	48 (25.9)	52 (28.1)	100 (27.0)
Ethnicity			
Hispanic	64 (34.6)	67 (36.2)	131 (35.4)
Non-Hispanic	121 (65.4)	118 (63.8)	239 (64.6)
Region			
Asia	57 (30.8)	60 (32.4)	117 (31.6)
Latin America	56 (30.3)	50 (27.0)	106 (28.6)
United States/Canada	37 (20.0)	38 (20.5)	75 (20.3)
Rest of world	35 (18.9)	37 (20.0)	72 (19.5)
Renal biopsy class			
Class III/III + V	32 (17.3)	26 (14.1)	58 (15.7)
Class IV/IV + V	124 (67.0)	128 (69.2)	252 (68.1)
Class V only	29 (15.7)	31 (16.8)	60 (16.2)
Scarring on renal biopsy‡	66 (35.7)	56 (30.3)§	122 (33.0)§
Serum creatinine, mean ± SD μmoles/liter; mg/dl	108.6 ± 1.2; 97.2 ± 1.1	92.7 ± 1.0; 56.9 ± 0.6§	100.6 ± 1.1; 80.0 ± 0.9§
Age, mean ± SD years			
At enrollment	32.4 ± 11.2	31.3 ± 10.3	31.9 ± 10.7
At diagnosis of lupus nephritis	30.2 ± 11.0	28.8 ± 10.2	29.5 ± 10.6
Time since diagnosis of lupus nephritis, median (range) years¶	1.0 (1–21)	1.0 (1–23)	1.0 (1–23)

* Except where indicated otherwise, values are the number (%) of patients treated with mycophenolate mofetil (MMF) or intravenous cyclophosphamide (IVC). Adapted, with permission, from ref. 21.
† Race self-reported as black (n = 46), Mexican-Mestizo (n = 28), mixed race (n = 9), Hispanic (n = 3), North African (n = 2), Chinese (n = 1), South/Central America/Caribbean (n = 3), Native American (n = 1), Pacific Islander (n = 1), Eritrean (n = 1), East Indian (n = 1), Middle Eastern (n = 1), Latin (n = 1), brown (n = 1), or white (n = 1).
‡ Scarring defined according to the International Society of Nephrology/Renal Pathology Society classification of class III/IV active/chronic lupus nephritis (23).
§ Data missing for 1 patient.
¶ Time since diagnosis was rounded up to 1.0 years for patients whose time since diagnosis was <1 year.

The immunologic end points studied were the levels of complement proteins C3 and C4 and total hemolytic complement CH50, and the titers of anti-dsDNA antibodies, which were assessed in 3 central laboratories (Quest Diagnostics Clinical Trials, Northridge, CA [for subjects in the US/Canada, Latin America, Malaysia, and Australia]; Quest Diagnostics Clinical Trials, Middlesex, UK [for subjects in Europe and South Africa]; and MDS Laboratories, Beijing, China [for subjects in China]). Normal ranges were defined as 90–180 mg/dl for C3, 16–47 mg/dl for C4 (low C4 was defined as a level <0.16 gm/liter in one laboratory and <0.10 gm/liter in the other laboratory, with each patient's baseline and end point samples analyzed at the same laboratory), and 26–58 units/ml for CH50. Anti-dsDNA values were grouped as follows: <30 IU/ml (negative), 30–60 IU/ml (low-positive), >60–200 IU/ml (positive), and >200 IU/ml (strong-positive).

Statistical analysis. Descriptive analyses of the data are presented. Analyses were conducted for all patients completing 24 weeks of induction treatment (per protocol). In addition, analyses of the data at end point were conducted in the ITT population, which comprised randomized subjects who had at least 1 postbaseline efficacy assessment (LOCF).

RESULTS

Participants and treatment. The demographic and baseline characteristics of the 370 randomized participants (ITT population; n = 185 in each group) were similar between the treatment groups (Table 1), as has been reported previously (21). Baseline BILAG index scores, SELENA–SLEDAI scores, and immunologic variables were also similar (results not shown).

At week 24, 306 patients (82.7%) remained in the study. Withdrawals included 35 patients (18.9%) in the mycophenolate mofetil group and 29 (15.7%) in the cyclophosphamide group. Reasons for noncompletion of the study in the mycophenolate mofetil and cyclophosphamide groups included adverse events (24 [68.6%] versus 13 [44.8%]), consent withdrawn (6 [17.1%] versus 5 [17.2%]), and other reasons (5 [14.3%] versus 11 [37.9%]) (21). Six patients in the ITT population (1 in the mycophenolate mofetil group and 5 in the

Table 2. Proportion of patients treated with MMF or IVC who failed to respond to treatment according to unchanged BILAG index scores at end point or week 24*

	MMF (n = 185)		IVC (n = 185)	
Data set, BILAG system	Baseline	End point	Baseline	End point
End point (LOCF)				
General	22	1 (4.5)	38	3 (7.9)
Mucocutaneous	56	9 (16.1)	51	7 (13.7)
Neurologic	3	1 (33.3)	5	1 (20)
Musculoskeletal	27	4 (14.8)	33	3 (9.1)
Cardiovascular/respiratory	8	2 (25)	12	0
Vasculitis	9	0	8	0
Renal	181	34 (18.8)	179	51 (31.8)
Hematologic†	62	25 (40.3)	74	28 (37.8)
Week 24 (completers)				
General	22	0	38	2 (5.3)
Mucocutaneous	56	7 (12.5)	51	2 (3.9)
Neurologic	3	0	5	0
Musculoskeletal	27	3 (11.1)	33	1 (2.9)
Cardiovascular/respiratory	8	2 (25)	12	0
Vasculitis	9	0	8	0
Renal	181	20 (11.1)	179	42 (23.5)
Hematologic†	62	18 (29.0)	74	18 (24.3)

* Values at baseline are the number of patients with a British Isles Lupus Assessment Group (BILAG) index score of grade A or B. Values at end point are the number (%) of patients whose BILAG score for the specified system remained a grade A or B, in the data analyses including patients who exited the study prior to week 24, for whom the end point comprised the last recorded value while on treatment (last observation carried forward [LOCF]), and in the data set in which the alternative end point was week 24 for those patients who completed 24 weeks of induction treatment. If no postbaseline value was available, the end point was considered missing. See Table 1 for other definitions.
† Data collected for the BILAG index hematologic domain should be interpreted with caution, since the results may reflect differences in adverse event profiles between the 2 comparator drugs, rather than systemic lupus erythematosus–driven changes.

cyclophosphamide group) were excluded from the safety analysis because they had not received the study drug.

The mycophenolate mofetil group received a mean ± SD dosage of 2.47 ± 0.58 gm/day (median 2.6 gm/day; n = 179) for a mean duration of 156.2 days. The maximum dosage (2.5–3.0 gm/day) was achieved in 91.3% of patients. The cyclophosphamide group received a mean ± SD dosage of 5.61 ± 1.10 gm/day (median 6.0 gm/day; n = 180) for a mean duration of 162.5 days. There was no statistically significant difference in corticosteroid tapering between the 2 treatment groups. The prednisone dosage was steadily decreased from day 1 (mean ± SD 54.46 ± 9.38 mg/day in the cyclophosphamide group and 51.78 ± 9.94 mg/day in the mycophenolate mofetil group) to weeks 22–24 (10.11 ± 2.96 mg/day and 9.94 ± 2.79 mg/day, respectively), which was consistent with the protocol-specified tapering schedule.

Disease activity assessed by the BILAG index. *Baseline.* Many patients had severe or moderate (BILAG index grade A or grade B) mucocutaneous, musculoskeletal, or hematologic disease activity at baseline, but due to the selection criteria, central nervous system involvement was rarely observed (Table 2 and Figure 1). The proportion of patients considered to have severe or moderate disease activity in the neurologic, cardiovascular/respiratory, or vasculitis systems at baseline was low in both treatment groups (Table 2). Therefore, only limited analysis was possible in these domains. The BILAG index scores at baseline indicated a predominance of severe renal involvement, with the majority of patients in both treatment groups having grade A renal disease (Figure 1).

End point (LOCF). There was an overall trend toward lower BILAG index scores in both treatment groups at the end point, reflecting a reduction in disease activity in both groups (Tables 2 and 3 and Figure 1). In both treatment groups and in all disease domains on the BILAG index, with the exception of the renal domain, comparable proportions of patients with a grade A or grade B at baseline achieved a grade D (no current activity) or a grade C or D (mild or no activity) at end point. In the renal domain, slightly more patients treated with mycophenolate mofetil than those treated with intravenous cyclophosphamide showed a reduction in disease activity between baseline and end point.

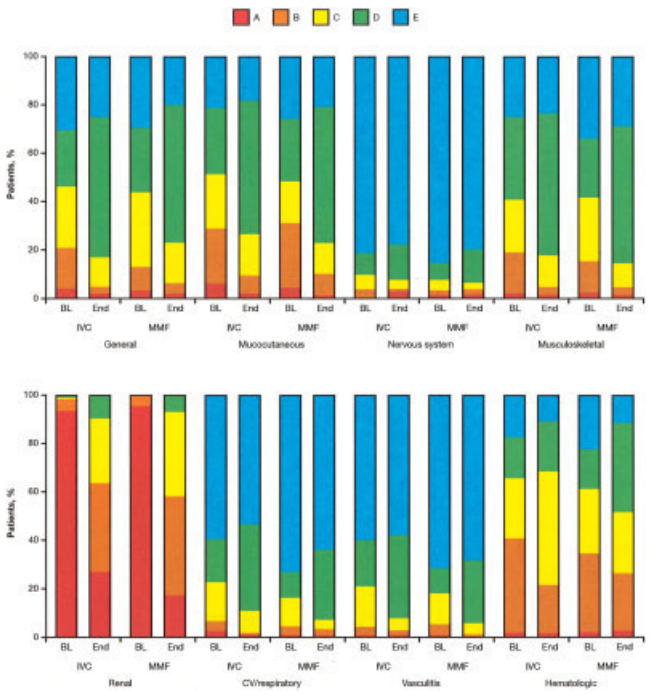

Figure 1. Distribution of British Isles Lupus Assessment Group (BILAG) index scores (BILAG grades A–E) in each of 8 domains at baseline (BL) and end point for patients treated with mycophenolate mofetil (MMF) or intravenous cyclophosphamide (IVC). Grade A = severe activity; grade B = moderate activity; grade C = mild activity; grade D = no current activity; and grade E = no activity ever. CV = cardiovascular.

Week 24 (completers). Remission (grade D on the BILAG index) was achieved in ~60% of patients whose initial score for the affected system (general, mucocutaneous, or musculoskeletal domain) indicated active disease. Furthermore, >70% of patients showed improvement in disease activity to at least a grade C (minimal activity) by week 24 (Table 3). Only small proportions of patients with a grade A or grade B at baseline still had this score at week 24 (Table 2).

Remission was achieved in each of the organs/systems assessed by the BILAG index. The majority of patients with a grade A or grade B at baseline went into remission by week 24 (achieving a grade C or grade D, indicating mild or no disease activity) or showed a clinically significant response and were no longer scoring a grade A or grade B at week 24, and this was consistent across all domains (Tables 2 and 3). Mycophenolate mofetil and cyclophosphamide had a similar profile of efficacy in each of the organs/systems, since both treatments had similar effects in most domains (Table 2).

At week 24, a reduction in the BILAG index to grade C or grade D was achieved in the mycophenolate mofetil and cyclophosphamide groups in the general domain (100% of 18 patients versus 93.5% of 31 patients, respectively), mucocutaneous domain (84% of 45 patients versus 93% of 43 patients, respectively), musculoskeletal domain (91% of 23 patients versus 96% of 26 patients, respectively), and hematologic domain (60% of 47 patients versus 67% of 55 patients, respectively) (Table 3). The data collected for the hematologic domain, however, should be interpreted with caution, since recorded activity may be a reflection of the differences in adverse event profiles between the 2 comparator drugs, rather than an indicator of SLE-driven changes, and appropriate attribution would therefore be difficult.

Flares assessed by the BILAG index on followup. Flares (defined as a new BILAG index score of grade A or grade B [severe or moderate disease activity] after a previous score of grade C, D, or E [mild, no current, or no previous disease activity, respectively]) were infrequent during the short followup period in the induction phase. Few patients scoring a grade C, D, or E at baseline had a grade A or grade B at week 24 in the same systems. In patients treated with mycophenolate mofetil, there were no such exacerbations in the neurologic, cardiovascular/respiratory, vasculitis, or renal domains, but worsening disease activity occurred in a few patients (in the general domain, change from grade C to grade B [n = 1]; in the mucocutaneous domain, change from grade C to grade B [n = 1], grade D to grade B [n = 3], and grade E to grade B [n = 1]; in the musculoskeletal

Table 3. Proportion of patients treated with MMF or IVC who responded to treatment according to improved BILAG index scores at end point or week 24*

Data set, BILAG system	MMF (n = 185)	IVC (n = 185)
End point (LOCF)		
General	21/22 (95)	33/38 (87)
Mucocutaneous	45/56 (80)	36/51 (71)
Musculoskeletal	23/27 (85)	30/33 (91)
Hematologic	33/62 (53)	44/74 (59)
Week 24 (completers)		
General	18/18 (100)	29/31 (93.5)
Mucocutaneous	38/45 (84)	40/43 (93)
Musculoskeletal	21/23 (91)	25/26 (96)
Hematologic	28/47 (60)	37/55 (67)

* Values are the number/total number (%) of patients with a British Isles Lupus Assessment Group (BILAG) index score of grade A or grade B at baseline who achieved a grade C or grade D BILAG index score for the specified system at end point, in the data analyses including patients who exited the study prior to week 24, for whom the end point comprised the last recorded value while on treatment (last observation carried forward [LOCF]), and in the data set in which the alternative end point was week 24 for those patients who completed 24 weeks of induction treatment. If no postbaseline value was available, the end point was considered missing. See Table 1 for other definitions.

domain, change from grade C to grade B [n = 1], and grade D to grade B [n = 1]). Worsening of disease activity in the hematologic domain (grade C to grade B [n = 8], grade D to grade B [n = 2], grade E to grade B [n = 4], and grade D to grade A [n = 1]) was also recorded, but these changes may reflect the occurrence of adverse events due to drug therapy, rather than a true increase in lupus activity.

In patients treated with intravenous cyclophosphamide, only the general domain was free from exacerbations, and worsening disease activity occurred in some patients in the mucocutaneous domain (change from grade C to grade B [n = 2], grade D to grade B [n = 1], and grade E to grade B [n = 1]), neurologic domain (grade D to grade B [n = 1]), musculoskeletal domain (grade C to grade B [n = 1], and grade D to grade B [n = 2]), cardiovascular/respiratory domain (grade E to A [n = 1]), vasculitis domain (grade C to grade B [n = 3], and grade E to grade B [n = 1]), and renal domain (grade C to grade B [n = 1]). Similarly, worsening of disease activity was seen in the hematologic domain (from grade B to grade A [n = 1], grade C to grade B [n = 4], grade D to grade B [n = 3], and grade E to grade B [n = 1]), but again, attribution of these changes to lupus is difficult to establish.

Disease activity assessed by the SELENA–SLEDAI. When changes in disease activity were assessed using the SELENA–SLEDAI, there was a shift toward lower disease activity in both treatment groups at week 12 that was sustained through week 24 or at end point. In the mycophenolate mofetil group, the mean ± SD changes in the SELENA–SLEDAI score from baseline (baseline score mean ± SD 14.7 ± 6.7, median 14.0) were −5.7 ± 7.0 at week 12 and −7.0 ± 7.6 at week 24 or −6.2 ± 10.1 at end point (Table 4). In the cyclophosphamide group, the mean ± SD changes from baseline (baseline score mean ± SD 15.9 ± 6.9, median 16.0) were −6.4 ± 7.3 at week 12 and −7.3 ± 7.6 at week 24 or −6.6 ± 7.9 at end point (Table 4). However, the SELENA–SLEDAI scores in both treatment groups appeared to be driven by the renal manifestations of SLE.

Scoring of the nonrenal manifestations of lupus nephritis by the SELENA–SLEDAI showed that in the mycophenolate mofetil group, the mean ± SD changes in nonrenal SELENA-SLEDAI scores from baseline (baseline score mean ± SD 5.8 ± 4.7, median 4.0) were −2.7 ± 4.7 at week 12 and −3.3 ± 4.5 (median −2.0) at week 24 or −2.6 ± 7.7 (median −2.0) at end point. In the cyclophosphamide group, the mean ± SD changes in the nonrenal SELENA–SLEDAI scores from baseline (baseline score mean ± SD 6.6 ± 4.8, median 6.0) were −3.2 ± 5.2 at week 12 and −3.9 ± 4.9 (median −3.0) at week 24 or −3.3 ± 5.2 (median −2.0) at end point.

Table 4. Mean changes in the Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index score from baseline to end point*

	Cyclophosphamide (n = 185)	Mycophenolate mofetil (n = 185)
Baseline		
No. of patients assessed	184	185
Mean ± SD total score	15.9 ± 6.89	14.7 ± 6.66
End point		
No. of patients assessed	178	179
Mean ± SD total score	9.2 ± 6.72	8.4 ± 8.71
Change from baseline to end point		
No. of patients assessed	178	179
Mean ± SD change in score	−6.6 ± 7.98	−6.2 ± 10.07
Treatment effect, difference in mean score change†		0.41
95% CI of difference		−1.48 to 2.30

* End point was defined as the last observation carried forward. If no postbaseline value was available, the end point was considered missing. 95% CI = 95% confidence interval.
† Difference between cyclophosphamide and mycophenolate mofetil in the mean change from baseline.

Overall, remission (SELENA–SLEDAI score ≤2) was achieved in 62 (17.4%) of the 357 patients assessed at end point. A larger number of patients in the mycophenolate mofetil group (34 [18.4%] of 185 patients) compared with those in the cyclophosphamide group (24 [13.0%] of 184 patients) had disease in remission at 24 weeks. Similarly, a larger proportion of patients in the mycophenolate mofetil group with high disease activity at baseline had mild or no disease activity (SELENA–SLEDAI score ≤2) at end point (34 [19.0%] of 179 patients in the mycophenolate mofetil group versus 21 [11.8%] of 178 patients in the cyclophosphamide group).

Flares were prevented. Only 2 patients experienced flares in disease activity, defined as an increase in the SELENA–SLEDAI score of ≥12 from baseline, during the 24 weeks of treatment. Both patients who experienced flares were in the cyclophosphamide group and were reported to have neurologic symptoms (seizure/lupus headache), as indicated by increased scores on the SELENA–SLEDAI and a corresponding BILAG score of grade A in the nervous system domain.

Changes in the SDI. Mean SDI scores for lupus-related damage were low at baseline in both the mycophenolate mofetil group and the cyclophosphamide group (mean SDI 0.5 versus 0.6), and there was no

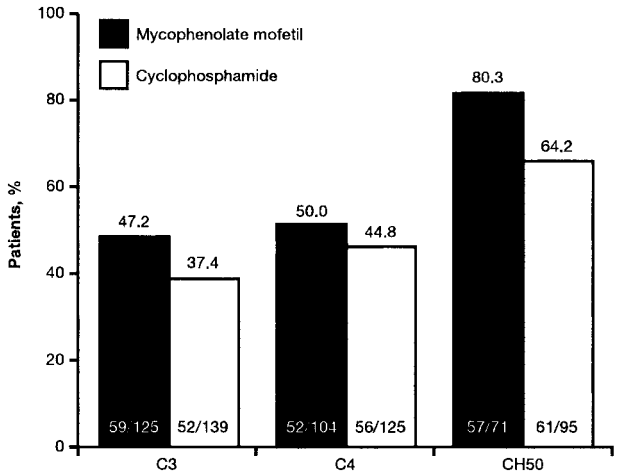

Figure 2. Proportion of patients who achieved normalization of their complement protein levels (C3, C4, and CH50) from baseline to end point following treatment with mycophenolate mofetil or intravenous cyclophosphamide, after displaying hypocomplementemia at baseline. Bars show the percentage of patients achieving normal levels at end point in each treatment group; also shown are the actual numbers of patients achieving normal levels among the total number assessed, and the actual percentage values over the bars. Normal ranges were 90–180 mg/dl for C3, 16–47 mg/dl for C4, and 26–58 units/ml for CH50.

increase in damage during the induction phase in either treatment group. At week 24 and at end point, the mean SDI scores were 0.5 in patients treated with mycophenolate mofetil and 0.6 in those treated with intravenous cyclophosphamide.

Changes in immunologic end points. For C3, C4, and CH50, there was an overall shift toward normal levels in both treatment groups at end point (Figure 2), consistent with a decrease in active disease. This improvement was evident at all time points assessed (baseline to weeks 4, 8, 12, 16, 20, and 24).

In addition, in both treatment groups, there was an overall shift toward lower titers of anti-dsDNA antibodies from baseline to end point, again suggesting that an improvement in disease activity had occurred. Thirty-nine percent of patients treated with mycophenolate mofetil (46 of 117) compared with 29% of patients treated with cyclophosphamide (36 of 124) had a positive or strong-positive anti-dsDNA antibody titer at baseline that subsequently fell to a low or negative titer at end point.

Safety. The safety data from the ALMS have been published in full elsewhere (16).

DISCUSSION

The heterogeneity of SLE makes it essential to assess the effects of therapies on all organ systems. For individual patients, any one of the various manifestations may be the greatest problem and could require the most aggressive treatment. To date, however, there have been few studies addressing the effect of the available therapies on specific manifestations. A therapy that is effective for one manifestation may not be effective for all manifestations. Indeed, a treatment that controls disease in one organ system might exacerbate disease elsewhere. Thus, hydroxychloroquine is often effective for the joint, skin, and fatigue manifestations of lupus but is rarely effective against other manifestations.

The current analysis provides valuable data on the effects of 2 of the most widely prescribed therapies for lupus nephritis: mycophenolate mofetil and cyclophosphamide. However, because the study was performed in patients with lupus nephritis, the results cannot be extrapolated to patients with nonrenal SLE. Moreover, although induction treatment for lupus nephritis with monthly intravenous cyclophosphamide is an accepted clinical practice (20), this agent is not the standard of care in patients with lupus who do not have renal disease. As an SLE-specific end point of disease activity, the BILAG index provides information on the body systems most commonly affected. These data, collected during the 24-week induction phase of the trial, showed that although mycophenolate mofetil and cyclophosphamide are often prescribed specifically to control lupus nephritis, these agents also have beneficial effects on disease activity elsewhere in the body. Most reassuringly, improvements in renal disease activity were rarely accompanied by exacerbation in any other organ system; in fact, clinically significant improvement was seen in all systems recorded by the BILAG index.

There appeared to be no clear difference in the efficacy of mycophenolate mofetil and cyclophosphamide as induction therapy for lupus nephritis in patients with extrarenal activity, for both renal and nonrenal manifestations of SLE. Since the current analysis was descriptive in nature, however, further investigation using appropriately designed studies will be necessary to determine whether mycophenolate mofetil and cyclophosphamide have different efficacy profiles among the various organ systems. For example, there could be differences in the time to response among organ systems, which might differ by treatment. Interestingly, both treatments were effective in the presence of a relatively fast steroid taper. Since steroids would normally be the initial therapy for the majority of extrarenal manifestations of SLE, the possibility of its influence on the efficacy in both treatment arms cannot be excluded, because steroids alone may have been adequate to control more minor disease manifestations.

Concomitant steroid administration may have also influenced response rates to mycophenolate mofetil in other studies (32–34).

Good rates of response to mycophenolate mofetil have been reported in 2 patients whose disease was refractory to treatment with cyclophosphamide and who were receiving mycophenolate mofetil (2 gm daily) and either intravenous pulse methylprednisolone (3 doses of 500 mg) (n = 1) or prednisolone (7.5 mg/day) and cyclosporin A (5 mg/kg/day) (n = 1) for hematologic manifestations (32,33). Remission was achieved in both cases during the 8–12 months of followup. Modest responses have been seen with intravenous pulse methylprednisolone (15 mg/kg) and mycophenolate mofetil (2 gm/day for 6 months, followed by 1 gm/day in 2 divided doses) for neuropsychiatric manifestations of SLE refractory to cyclophosphamide (34). Of 3 patients treated with intravenous methylprednisolone pulses (15 mg/kg) for 3 days, followed by oral prednisolone (0.6 mg/kg/day for 6 weeks, then tapered by 5 mg/week until reaching a dosage of <10 mg/day) and mycophenolate mofetil (2 gm/day for 6 months, followed by 1 gm/day in 2 divided doses), 2 patients responded partially, whereas 1 had complete clinical recovery.

The current data showing that mycophenolate mofetil reduces disease activity in the systems covered by the BILAG index support the results in previous studies (15). A systematic review of observational data showed that mycophenolate mofetil was effective for refractory hematologic (n = 10) and dermatologic (n = 16) manifestations of SLE, whereas the response of patients with neurologic manifestations (n = 7), although confounded by concurrent medications, was mixed (15). The current data extend these observations, with an 88% response rate in the BILAG index mucocutaneous domain (n = 56), 100% response rate in the general domain (n = 22), and 89% response rate in the musculoskeletal domain (n = 27) (Table 2). In terms of the response in immunologic variables, the current data support previous reports of reduced anti-dsDNA antibody titers (15,16) and increased complement C3 levels (16).

Although the current data support the efficacy of mycophenolate mofetil and cyclophosphamide on a variety of affected systems in patients with lupus nephritis, further studies are needed to confirm these observations. The BILAG index was not the primary end point measure in the ALMS, and therefore care needs to be taken to avoid overinterpretation of the findings. Furthermore, division of this secondary end point into the different body systems limits the power of each subscale, although this was a predetermined analysis; this is particularly true for categories with low sample sizes (e.g., the neurologic domain). The trial assessed a substantial number of patients, but patients with the most severe lupus were excluded (e.g., those with severe neurologic disease or those who had received pulsed steroid treatment), and the current analysis focused only on the effects up to 24 weeks of treatment.

Thus, the present study provides valuable data on the effects of 2 of the most commonly prescribed therapies for severe SLE on nonrenal lupus activity. The findings of this study should be interpreted as being applicable only to patients with lupus nephritis with concurrent extrarenal disease activity, and may not be generalized to SLE patients without renal disease. Although the analysis does not reveal any differences in efficacy between mycophenolate mofetil and cyclophosphamide, the data are of interest because they imply that both drugs have efficacy in treating nonrenal manifestations in patients with lupus nephritis, when the effects are assessed in a formal randomized controlled trial using a large and ethnically diverse population. Further clinical trials assessing the safety and efficacy of mycophenolate mofetil in patients with poorly controlled nonrenal manifestations of lupus are warranted.

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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. Ms Lisk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ginzler, Wofsy, Isenberg, Gordon, Lisk, Dooley.

Acquisition of data. Ginzler, Lisk.

Analysis and interpretation of data. Ginzler, Wofsy, Gordon, Lisk, Dooley.

ROLE OF THE STUDY SPONSOR

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