EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2015.0048

Original Investigation

Impact of standard of care treatments and disease variables on outcomes in systemic lupus erythematosus trials: analysis from the Lupus Foundation of America Collective Data Analysis Initiative

Kenneth Carekin Kalunian[1], Mimi Kim[2], Xianhong Xie[2], Amrutha Baskaran[1], Rossi Paola Daly[3], Joan Tenenbaum Merrill[4]

Abstract

Objective: Most clinical trials for systemic lupus erythematosus (SLE) study the efficacy and safety of investigational agents added to variable background immunosuppressants, which has resulted in high response rates in patients treated with placebo plus standard of care (SOC) plus rescue measures. This project compared the impact of different SOC treatments and disease variables on the outcomes of SLE trials.

Material and Methods: Data were obtained from 981 patients receiving only SOC treatments in three nephritis and three general SLE trials to compare response and flare rates on the basis of the British Isles Lupus Assessment Group (BILAG) index, a measure common to all trials.

Results: For subjects enrolled in general SLE trials (n=173), those receiving mycophenolate mofetil (MMF) had more severe baseline disease, included more patients of African descent, and were administered higher baseline steroid doses compared with those receiving azathioprine (AZA) or methotrexate (MTX). BILAG responses at week 12 were MMF 35%, AZA 49%, MTX 34%, and no immunosuppressant (NIS) 65%. At week 52, MMF response rates increased to 41% despite reducing the steroid doses, but fell in all others (p=0.07, adjusted for steroids). Patients with severe disease activity at baseline (SDAB) who were defined as ≥1 BILAG A (severe) organ score had lower response rates to AZA or MTX but higher rates to MMF or NIS. Interim flares were highest with MMF [flares/patient–year (pt–yr)]. For all flares, rates were as follows: AZA 1.24, MMF 1.87, MTX 1.42, and NIS 0.81 and severe flares were as follows: AZA 0.66, MMF 1.29, MTX: 1.20, and NIS 0.55. Interim flares occurred in 71% of MMF-endpoint responders, 54% of AZA, 50% of MTX, and 22% of NIS. Patients with SDAB had more flares than moderate patients in the MMF and MTX groups: MMF: 2.39 vs. 1.03 flares/pt–yr (p=0.01), MTX: 2.33 vs. 0.63 (p=0.0002), severe flares: 1.87 vs. 0.34 for MMF (p=0.0013), 2.13 vs. 0.40 for MTX (p<0.0001). In nephritis trials (n=808), MMF subjects received less steroids than intravenous cyclophosphamide and response rates were similar, but MMF-treated patients had fewer severe flares (p=0.03).

Conclusion: Compared with MMF, AZA and MTX were associated with lower response rates at week 52. AZA-treated subjects had fewer flares and remained more stable in trials while engendering lower placebo plus SOC responses. MMF-treated subjects had frequent responses but more flares, suggesting that flares should be included in endpoint definitions. Given the likelihood of treatment selection bias, these data do not provide conclusions regarding efficacy but may help future trial designs by distinguishing factors definable at entry that are predictive of outcomes.

Keywords: Systemic lupus, clinical trials, immunosuppressants

1 Department of Medicine, University of California San Diego, La Jolla, California, USA

2 Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, New York, USA

3 Department of Education and Research, Lupus Foundation of America, Washington, District of Columbia, USA

4 Clinical Pharmacology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA

Address for Correspondence: Kenneth Carekin Kalunian, Department of Medicine, University of California San Diego, La Jolla, California, USA

E-mail: kkalunian@ucsd.edu

Submitted: 30.06.2015
Accepted: 18.08.2015
Available Online Date: 29.01.2016

Copyright 2016 © Medical Research and Education Association

Introduction

In the past decades, many investigational agents for systemic lupus erythematosus (SLE) have failed to meet the endpoints of phase II or III clinical trials. Exploratory analysis of completed studies suggests that disparate background immunosuppressant regimens, which are allowed as a background therapy in these trials, interfere with the discrimination between investigational agents and placebo (1-3). Unresolved questions regarding the impact of standard treatments on an already heterogeneous population have decreased the confidence in whether the treatments or trial designs have failed.

Data suggests that when targeted biologics are tested in a multifactorial disease, there could be a maximum ceiling effect of 40%–50% on the potential response rates (4-6). Therefore, it would be optimal if the background and rescue medications did not themselves approach 40% efficacy when administered in placebo groups. Presumably, standard of care (SOC) treatments are not interchangeable, and on the basis of the clinical practice and experience, these treatments are not administered to identical types of patients. Thus, some SOC treatments may be associated with greater response rates in some trials than in others despite (or even because of) a treatment selection bias being inherent in including patients with respect to the various background treatments. To examine this hypothesis, a data repository was required from substantial numbers

of patients who had participated in clinical trials and who had received only SOC treatments.
The Collective Data Analysis Initiative (CDAI) comprises clinical investigators who work in designing, execution and the analysis of biopharmaceutical clinical trials in SLE. An initial data repository was collected from six completed registered clinical trials, including placebo groups from five biological trials and one study in which two standard treatments were compared. Differences in the populations who were included in these trials on different treatments were evaluated, and the response and flare rates in these groups were compared.

Material and Methods

De-identified data from patients treated with SOC in six multicenter, randomized, placebo-controlled phase II or III clinical trials were combined as part of CDAI (7), resulting in data from 993 subjects with an international mixture of races, cultures, and local treatment standards. The ethic committees' approvals were obtained according to local regulations, and informed consent procedures were completed in accordance with the Helsinki Declaration version that was in effect at the time of each trial. Three of the trials enrolled SLE patients with active disease but without acute nephritis (general SLE), and the other three trials enrolled patients suitable for nephritis-induction treatment. The following SOC medication groups were evaluated in general SLE trials: azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), or no immunosuppressant (NIS). Nephritis trials compared MMF vs. intravenous cyclophosphamide (IVC). Subjects in all groups received variable use and dosage of antimalarials and/or corticosteroids but no biological therapies.

Clinical endpoints were restricted to variables provided across all studies. The classic British Isles Lupus Assessment Group (BILAG) index was used because it was the only common instrument (8). This index is a sensitive measure that can capture partial or complete improvement in SLE. For general SLE, BILAG response was defined by at least one gradation improvement in any BILAG A (severely active) and/or B (moderately active) organ compared with baseline, without a significant new disease (at least 1 A or 2 Bs). Organ-specific responses in mucocutaneous and musculoskeletal systems were evaluated as at least one gradation of improvement in that organ. In nephritis trials, response was defined as an improvement in a renal BILAG A or B to BILAG C (mild disease) or better, with improvement by at least 1 grade in all baseline extra-renal BILAG As or Bs and no new BILAG A or ≥2 new Bs at the time of assessment. Severe flare was defined as the occurrence of at least one new BILAG A since the previous visit; a flare of any type was defined as ≥1 new A or 2 new B organ scores. Recent BILAG definitions of flare (9) could not be employed because of a lack of data regarding individual descriptors.

Analysis of variance and t-tests were used to evaluate differences in continuous variables between the treatment groups, and the chi-square or Fisher's exact tests were performed for binary outcomes, such as response status. Logistic regression models were fit to the data to compare response rates that were adjusted for steroid dose. Flare rates were estimated and compared between groups using Poisson regression methods to account for the occurrence of multiple flares per person. Analyses were performed using SAS software, version 9.4, (SAS Institute Inc., Cary, North Carolina, USA). A two-sided p value <0.05 was considered statistically significant.

Results

Baseline characteristics of pooled clinical trial populations

In the combined database, the mean age of patients at baseline was 32.9±10.9 years with disease duration of 4.7±5.4 years. As expected, most of the enrolled patients were women (88%). The racial composition in general SLE trials was 63% European, 17% African, 13% Asian, and 11% other backgrounds. Patients in nephritis trial were 43% European, 10% African, 34% Asian, and 13% other.

The evaluation of general SLE was separately performed from nephritis-induction trials because these types of trials are universally independently performed. In general SLE trials, MMF-treated patients received a slightly higher baseline mean dose of steroids (39.0±23.2) than other groups (Table 1); however, in nephritis trials, the steroid dose at baseline was lower in MMF-treated patients than in IVC-treated patients (20.3±25.8 vs. 34.0±75.3; p=0.002). In both the general and nephritis trials, there were more patients of African descent in the MMF group than in the other treatment groups, and this was more pronounced in the non-nephritis trials. Other than these racial differences, discrepancies in the demographics were surprisingly minimal. Patients in nephritis trials had shorter mean disease duration than patients in general SLE trials, and within the latter population, MTX-treated patients had shorter mean disease duration than other immunosuppressant-treated patients (Table 1).

In general SLE trials, 64% of MMF-treated patients had at least one organ at baseline with severe disease (BILAG A) vs. 53% of AZA-treated patients, 52% of MTX-treated patients, and 58% of NIS-treated patients. In nephritis trials, 94% of MMF-treated and 96% of IVC-treated patients had at least one BILAG A at baseline. Thus, MMF-treated patients in nephritis trials appeared well matched to IVC-treated patients, i.e., those receiving the alternative SOC treatment, but may have received lower steroid doses at baseline.

Impact of treatment, steroid use, and disease severity on outcomes

In general SLE trials, corticosteroid doses remained slightly higher in MMF-treated patients at week 12 (MMF, 27.6 mg; AZA, 24.3 mg; MTX, 23.6 mg; NIS, 17.8; p=0.0001) but decreased in all groups by week 52 (MMF, 12.6 mg; AZA, 13.0 mg; MTX, 7.2 mg; NIS, 6.6; p=0.055) (Table 2). BILAG response at week 12 was observed in 35% of MMF vs. 49% of AZA, 34% of MTX and 65% of NIS (p=0.02 adjusted for steroid dose). At week 52, after all groups had substantially reduced steroids, the response rates increased to 41% in the MMF-treated group, remained high in the NIS group (48%), and decreased in the AZA and MTX-treated groups to 35% and 28%, respectively (p=0.07 adjusted for steroid dose).

Nephritis-induction trial data were available for 12 and 24 weeks after baseline. At week 12, 24% of patients met the BILAG endpoint with a mean prednisone equivalent dose of 36.5 mg/day. At week 24, the response rate increased to 33%, and the mean steroid dose was lowered to 14.5 mg/day (Table 2). There was no response difference between IVC and MMF (33% response for MMF and 31% for IVC; p=0.63 adjusted for corticosteroids) (Table 2). Furthermore, steroid doses were almost identical by the endpoint (Table 2) despite the fact that IVC-treated patients received more steroids at baseline.

Organ-specific response in non-nephritis trials

To understand whether organ-specific analyses may clarify data from lupus trials, SOC impact on the two most common non-renal organs was evaluated. In general SLE trials, mucocutaneous BILAG responses at week 52 were high in all SOC groups (54% of AZA-; 46% MMF; 47% MTX-; and 48% NIS-treated patients; p=0.95 adjusted for corticosteroids). Musculoskeletal improvements were also frequent at week 52 (54% AZA-, 59% MMF-, 45% NIS-, and only 28% MTX-treated patients; p=0.08 after corticosteroid adjustment) (Table 3).

Table 1. Demographics at baseline by standard of care medications

	Non-Nephritis trials						Nephritis trials			
	AZA	MMF	MTX	NIS	Total	p	IVC	MMF	Total	p
Total number	47	36	42	48	173		321	487	808	
Race										
European	29 (62%)	17 (47%)	29 (69%)	34 (71%)	109 (63%)		125 (39%)	220 (45%)	345 (43%)	
African	10 (21%)	11 (31%)	6 (14%)	3 (6%)	30 (17%)	0.07	27 (8%)	57 (12%)	84 (10%)	0.04
*Asian	5 (11%)	4 (11%)	4 (10%)	10 (21%)	23 (13%)		118 (37%)	155 (32%)	273 (34%)	
Other	3 (6%)	4 (11%)	3 (7%)	1 (2%)	11 (6%)		51 (16%)	55 (11%)	106 (13%)	
% Female	89%	92%	90%	98%	92%	0.34	85%	88%	87%	0.20
Age (Mean±SD)	38.5±13.2	38.7±12.4	41.7±12.5	39.0±10.4	39.4±12.1	0.58	31.6±9.9	31.1±10.0	31.3±9.9	0.43
Disease duration (Mean±SD)	10.6±8.5	9.3±7.9	5.5±4.3	N/A†	8.7±7.6	0.04	4.9±5.8	5.6±5.6	5.3±5.7	0.09
% with BILAG A at baseline	53%	64%	52%	58%	57%	0.71	96%	94%	94%	0.22
Steroid dose‡ (Mean±SD)	33.7±20.7	39.0±23.2	34.9±23.5	21.7±11.6	31.8±20.9	0.001	34.0±75.3	20.3±25.8	25.6±51.5	0.002

AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; IVC: intravenous cyclophosphamide; NIS: no immunosuppressant; SD: standard deviation

*Includes Asian, Pacific Islanders, and American Indians.

†N/A denotes not available.

‡Steroid dose includes IV and oral doses.

Flare rates

In general SLE trials, flare rates were highest in MMF-treated patients and lowest in NIS-treated patients (Table 4). Overall flare rates (any new BILAG A or >/=2 new Bs since the last visit) were higher in MMF-treated than AZA-treated patients after adjustment for corticosteroids (1.87 flares/pt–yr vs. 1.24 flares/pt–yr, p=0.04). MTX flare rate was 1.42 flares/pt–yr. Severe flare rate (any new A since last visit) was 0.66 flares/pt–yr in the AZA group, which is significantly lower than the rates in the MMF (1.29 flares/pt–yr; p=0.01) and MTX groups (1.20 flares/pt–yr; p=0.02) Organ-specific flare rates were marginally more frequent in the MMF and MTX groups than in the AZA group (Table 3).

Because many patients who participated in general SLE trials had only moderate disease, SOC response rates were compared between those with severe disease at baseline, (≥1 BILAG A score, Table 5a) vs. moderate baseline disease. In the AZA and MTX groups, patients with severe baseline scores had lower response rates, but these differences were not statistically significant. The opposite was observed in patients treated with MMF or NIS; those with more severe disease were more likely to respond in both of these groups. The MMF and NIS groups received the highest and lowest doses of steroids, respectively, through week 12 (Table 1, 2) and also had the most and least overall and severe flare rates, (Table 4), suggesting that they represent the most and least severely ill subsets.

At week 52, a high proportion of responders experienced interim flares in the earlier months of follow-up (71% of MMF, 54% of AZA, and 50% of MTX responders). Overall and severe flare rates were higher among MMF-treated patients with severe disease at baseline compared with moderate disease (overall flares: 2.39 vs. 1.03 flares/pt–yr, p=0.01; severe flares: 1.87 vs. 0.34 flares/pt–yr; p=0.0013). Flare rates were also higher in MTX-treated patients with severe vs. moderate disease at baseline (overall flares: 2.33 vs. 0.63 flares/pt–yr, p=0.0002; severe flares: 0.40 vs. 2.13 flares/pt–yr; p<0.0001) (Table 5b).

In nephritis trials, the response rates were similar in patients treated with MMF and IVC regimens (Table 2). Flare rates were also not significantly different (1.22 flares/pt–yr in the MMF group and 1.34 in the IVC group, p=0.23). However, MMF-treated patients had fewer severe flares (1.02 in the MMF group compared with 1.23 in the IVC group, p=0.03) (Table 4), an endpoint rarely examined in nephritis trials.

Discussion

Various possibilities can explain the repeated disappointments in trials of biologics that were developed for SLE (1-3). It is possible that not only have all the treatments been ineffective (except belimumab) but also that the heterogeneity of SLE confuses the interpretation of data for finely targeted agents that are appropriate for only certain patient subsets. Endpoints may be too sensitive, reflecting clinically unimportant changes. Background treatments may be more aggressive than necessary in some patients at the moderate end of the disease spectrum, thus, increasing the risk of high responses in those treated with placebo plus SOC.

The data reported here suggests a high rate of interim flares on SOC medications that then resolve by the end of a study. This erratic result phenomenon is invisible in landmark analysis at week 52, which is the most common primary endpoint for lupus trials. It seems logical that measuring flares during trials may help to better define the response and non-response and may provide a more interpretable endpoint. This approach has been used in the past, but in several cases, such as with rituximab and abatacept, it did not differentiate these investigational agents from placebo in early pivotal studies (8, 9). However, this may have been because of a problematic definition of flare in those studies. In the cases of ritubimab and atabacept studies, only one BILAG B score occurring even transiently at any time in those 52-week trials were defined as total non-re-

Table 2. Response rates and steroid dose by treatment
Treatment [Mean corticosteroid (CS) dose expressed as prednisone equivalent in mg]

	Week 12		Week 52	
Endpoint date	% Responders	Mean CS dose	% Responders	Mean CS dose
Non-nephritis trials				
Overall (n=168)	47	22.9	38	9.8
AZA (n=45)	49	24.3	35	13
MMF (n=34)	35	27.6	41	12.6
MTX (n=41)	34	23.6	28	7.2
NIS (n=48)	65	17.8	47	6.6
p value				
Unadjusted	0.01	0.001	0.35	0.055
Adjusted for CS dose	0.02		0.07	
	Week 12		Week 24	
Endpoint date	% Responders	Mean CS dose	% Responders	Mean CS dose
Nephritis trials				
Overall (n=770)	24	36.5	33	14.5
MMF (n=461)	26	36.4	33	13.9
IVC (n=309)	21	36.7	31	15.4
p value				
Unadjusted	0.11	0.80	0.49	0.02
Adjusted for CS dose	0.13		0.63	

AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; IVC: intravenous cyclophosphamide; NIS: no immunosuppressant

Table 3. Response and flare rates in mucocutaneous and musculoskeletal systems by treatment (non-nephritis trials)

Treatment	% Responders	p value with steroid adjustment	Total Person–years	Total flares*	Rate of flares	p
Musculoskeletal						
AZA	54	0.08	26.1	6	0.23	Reference
MMF	59		23.9	13	0.54	0.08
MTX	28		27.6	24	0.87	0.004
NIS	45		14.8	5	0.34	0.52
Mucocutaneous						
AZA	54	0.95	24.4	4	0.16	Reference
MMF	46		24.7	11	0.45	0.09
MTX	47		16.1	8	0.50	0.07
NIS	48		16.6	7	0.42	0.13

AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; NIS: no immunosuppressant
*Definition of severe flare: new A in that organ since last visit.

sponse, despite the fact that intermittent rashes and arthritis, which met minimal definitions for Classic BILAG B, may be common and would usually be considered clinically inconsequential if quickly resolved without treatment (1). Most patients in both the treatment and placebo groups in both of these early studies were, thus, rendered non-responders (8, 9), even if they were doing well for most of the year as suggested by their disease activity scores (9).

Two international phase III trials of belimumab in general SLE were more successful in discriminating between the treatment and placebo (4, 5). These trials applied a composite index (10) to a landmark analysis at week 52, making it impossible for any interim flare that subsequently resolved before the endpoint date to have any effect on the outcome. In this composite SLE response index (SRI), one BILAG B at week 52 also had no impact on the endpoint because a minimum of two new BILAG B scores was required to define non-response, thus, supplying a more stringent threshold for a clinically significant event.

Despite the ultimate success of the belimumab program, the landmark analysis coupled with aggressive SOC adjustments allowed in these trials led to high placebo group response rates, requiring the enrollment of large numbers of patients to gain traction from a modest treatment effect size. An exploratory analysis of patients with higher disease activity at baseline suggested lower response rates with placebo plus SOC in these sicker patients (11), as is suggested by the data reported here. Several analyses have confirmed that subsets of SLE patients, definable by serology, race, or disease activity as likely to be more ill and have less response to SOC even in aggressively treated placebo groups (8, 9, 12-14). Additional data suggest that less aggressive background treatments can lower response rates in moderately ill SLE patients (7-9, 15, 16), leaving room to determine whether a targeted treatment with potential ceiling response rate of 40%–50% may be effective.

The highest response rates to SOC in the current analysis were in MMF-treated patients. These patients also received more steroids for the first 12 weeks. Is this an overly treated group or does the treatment choice of MMF also define a more ill subset of patients who required those steroids? The higher flare rates in MMF-treated patients suggest the latter probability and the likelihood that fewer responses would be observed if the flares were factored into the analysis. The

Table 4. Analysis of flare rates by treatment

Treatment	Total person–years	Total flares*	Rate of flares	p†	Total severe flares*	Rate of severe flares	p†
Non-nephritis trials							
AZA	36.2	45	1.24	Reference	24	0.66	Reference
MMF	30.9	58	1.87	0.04	40	1.29	0.01
MTX	32.5	46	1.42	0.53	39	1.20	0.02
NIS	30.9	25	0.81	0.09	17	0.55	0.56
Nephritis trials							
MMF	343.7	420	1.22	Reference	351	1.02	Reference
IVC	193.6	260	1.34	0.23	238	1.23	0.03

AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; IVC: intravenous cyclophosphamide; NIS: no immunosuppressant

*Total flares were defined as any new A or ≥2 new Bs since previous visit.

Severe Flare was defined as any new A since last visit.

†By fitting a Poisson regression model to the total number of flares and the total person-years.

Table 5a. Response rates by baseline disease severity

	Week 52		
	% Responders If No BILAG A	% Responders If ≥1 BILAG A	p
AZA (n=37)	42 (n=19)	28 (n=18)	0.48
MMF (n=34)	31 (n=13)	48 (n=21)	0.50
MTX (n=36)	32 (n=19)	24 (n=17)	0.72
NIS (n=38)	31 (n=16)	59 (n=22)	0.11

AZA: azathioprine MMF: mycophenolate mofetil MTX: methotrexate NIS: no immunosuppressant; BILAG: British Isles Lupus Assessment Group

NIS group also had a high response rate while being treated less aggressively with no immunosuppressants and less steroids. However, they may have been less fundamentally ill at baseline despite their BILAG scores, which is supported by the fact that they had fewer interim flares. Importantly, the trials in the current analysis mandated aggressive steroid use, thus, even the lower doses administered to the NIS group may have been excessive for those patients, an issue less relevant to more recent trials in lupus. These data suggest important implications for trial design: optimal results for a SOC group may depend on how ill the patient is, how to treat aggressively enough for safety but not to an extreme, and how response is defined, whether by a landmark improvement endpoint or by factoring in interim flares.

A composite endpoint requiring improvement at a landmark date coupled to a lack of clinically significant flares over time may provide a feasible and discriminatory endpoint for trials. In an exploratory analysis of the rituximab explorer study, a similar approach requiring improvement at 6 months and subsequent lack of BILAG A (severe) flares did appear to distinguish the treatment from placebo in a trial mandating high-dose background steroids coupled with immunosuppressants, in which a third of the patients were administered MMF (16). This design would need to be prospectively tested but may be useful for trials of sicker patients.

In nephritis trials, MMF-treated patients received less steroids at baseline than IVC-treated patients. This could reflect combining populations from differing trial designs and should not be over-interpreted. However, while receiving less steroids, MMF-treated patients achieved equal overall response rates and developed fewer severe flares. Because there has been difficulty in differentiating treatment effects in nephritis trials, a combined endpoint incorporating interim BILAG flares with landmark renal response may be evaluated both in SOC comparisons and when adding biologics. In non-nephritis trials, the MMF group was slightly enriched for patients of African descent, presence of at least one BILAG A, and higher steroid doses, arguably a sicker group of patients compared with those receiving alternative treatments. AZA-treated patients had higher rates of early responses during the rescue phase but lost this high rate response at week 52 after reducing the steroid dose. Nevertheless, they also had lower flare rates and lower severe flare rates during that process. This information may help to design background treatment rules, define response definitions, and power optimal trials going forward.

There are limitations of the analyses that could be performed on the initial data obtained, which was derived from earlier lupus trials. Some of the trials mandated aggressive background steroids, which are a design no longer used; some did not provide sufficient data to examine current endpoints, such as SRI (10) and BILAG-linked Combined Lupus Assessment (BICLA) (6). The latest version of BILAG was also not in use nor was individual descriptor data available to assess newer BILAG flare definitions (17). Nevertheless, the results reported here did capitalize on the common use in these trials of the well-validated classic BILAG index (8), which is a sensitive and useful instrument, and may provide some solid preliminary insight into relative response and flare rates for patients receiving SOC in lupus studies. As more trials accumulate in this database, the analyses should become more robust.

The growing CDAI database may support adequate power to detect clinically meaningful data from rare subsets of trial participants and facilitate the development of new definitions of response and/or flare to moderate

Table 5b. Interim flares by baseline disease severity

Treatment	Baseline disease severity	Total person–years	All flares*	Rate of all flares	p†	Severe flares*	Rate of severe flares	p†
MMF	No A	11.7	12	1.03	Reference	4	0.34	Reference
	≥1 A	19.3	46	2.39	0.01	36	1.87	0.0013
AZA	No A	19.5	23	1.18	Reference	9	0.46	Reference
	≥1 A	16.8	22	1.31	0.72	15	0.90	0.12
MTX	No A	17.5	11	0.63	Reference	7	0.40	Reference
	≥1 A	15.0	35	2.33	0.0002	32	2.13	<0.0001
NIS	No A	11.4	10	0.88	Reference	5	0.44	Reference
	≥1 A	19.5	15	0.77	0.75	12	0.62	0.52

AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; NIS: no immunosuppressant

Response Definition: Non-nephritis trials: all baseline British Isles Lupus Assessment Group (BILAG) severe or moderate (A or B) scores improved by at least 1 step with no new A or 2+ new B scores.

*All flares defined as ≥1 new BILAG A or ≥2 new B scores any new A or ≥2 new Bs since the last visit. Severe flare defined as ≥1 new BILAG A since last visit.

†By fitting a Poisson regression model to the total number of flares and the total person–years for each background drug group.

the impact of SOC background medications on outcomes. Once a wider range of data are available, this evolving database should assist in clinical trial design by providing information on optimal background and rescue treatments for discrete populations, thus, allowing appropriate mitigation of serious disease activity during trials without obfuscating endpoints with high rates of response in the placebo groups.

Ethics Committee Approval: Data used in this analysis was obtained from trials that received Ethics Committee approvals in accordance to local regulations.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.K., M.K., J.T.M.; Design - K.K., M.K., J.T.M.; Supervision - K.K., M.K.; Materials - K.K., M.K., J.T.M., A.B., R.P.D.; Data Collection and/or Processing - K.K., M.K., J.T.M., A.B., R.P.D.; Analysis and/or Interpretation - K.K., M.K., J.T.M., A.B., R.P.D.; Literature Review - K.K., M.K., J.T.M., R.P.D., A.B.; Writer - K.K., M.K., J.T.M., R.P.D., AB.; Critical Review - K.K., M.K., J.T.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: Dr. Kalunian received consulting fees and grants from the following companies: Bristol Myers Squibb, Genentech, EMD Serono, Biogen IDEC, and UCB. Dr. Kalunian was on the Data Safety Monitoring Boards for EMD Serono. Dr. Merrill is the Medical Director of the Lupus Foundation of America and reports all the grants and personal fees obtained from the Lupus Foundation of America, Bristol Myers Squibb, EMD Serono, and UCB and all the personal fees from Genentech and Biogen IDEC, which are outside the submitted work.

References

1. Bruce IN, Gordon C, Merrill JT, Isenberg D. Clinical trials in lupus: what have we learned so far? Br J Rheumatol 2010; 49: 1025-7. [CrossRef]
2. Steinman L, Merrill JT, McInnes IB, Peakman M. Optimization of current and future therapy for autoimmune diseases. Nat Med 2012; 18: 59-65. [CrossRef]
3. Kalunian K, Merrill JT. New directions in the treatment of systemic lupus erythematosus. Curr Med Res Opin 2009; 25: 1501-14. [CrossRef]
4. 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. [CrossRef]
5. 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. [CrossRef]
6. Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M, et al. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis 2014; 73: 183-90. [CrossRef]
7. The Lupus Foundation of America. LFA collective data analysis initiative (CDAI). Available from http://www.lupus.org/CDAI
8. Hay EM, Bacon PA, Gordon C, Isenberg DA, Maddison P, Snaith ML, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med 1993; 86: 447-58.
9. Isenberg DA, Allen E, Farewell V, D'Cruz D, Alarcón GS, Aranow C, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis 2011; 70: 54-9. [CrossRef]
10. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in patients with moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010; 62: 222-33. [CrossRef]
11. Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010; 62: 3077-87. [CrossRef]
12. 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. [CrossRef]
13. 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. [CrossRef]
14. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol 2014; 66: 379-89. [CrossRef]

15. Furie RA, Leon G, Thomas M, Petri MA, Chu AD, Hislop C, et al. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. Ann Rheum Dis 2015; 74: 1667-75. [CrossRef]
16. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012; 64: 1215-26. [CrossRef]
17. Merrill JT, Immermann FW, Zhou T, O'Toole M, Whitley M, Hill AA, et al. Topline results of the Biomarkers of Lupus Disease (BOLD) study: clinical and mechanistic perplexities of lupus treatment trials can be mitigated by eliminating background immune suppressants. Arthritis Rheum 2013; 65 Suppl 10: 1809.