A comparison of rheumatoid arthritis and systemic lupus erythematosus trial design: a commentary on ways to improve the number of positive trials in SLE

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Abstract

Objectives

Recent systemic lupus erythematosus (SLE) randomised controlled trials (RCTs) were examined for potential design flaws and compared to rheumatoid arthritis (RA) RCT over the same time period to suggest modifications to SLE RCTs that could help improve the potential success rate of future SLE trials.

Methods

RA and SLE biologics RCTs published between 2005 and July 2013 were identified using PubMed. Inclusion criteria, study design, outcome measures, sample size calculations, patient baseline characteristics steroid use in the protocol and results were extracted and compared.

Results

All trials required active disease for enrolment. Twenty-two RA RCTs and eight SLE RCTs were included. All RA RCTs used either a partial or continuous measure of improvement. SLE RCTs used SLEDAI, BILAG, SLAM, SRI and BICLA. RA trials were larger (543 vs. 376 participants). Concomitant corticosteroid use was stable in 100% of RA trials while all SLE RCTs allowed dose tapering. RA trials were mostly in methotrexate or DMARD inadequate responders whereas SLE trials allowed for the presence or absence immunosuppressives within all trials. Sample sizes in RA were determined on a change in disease activity or proportion meeting a disease state. Positive trials were found in 100% of RA RCTs and 25% of SLE RCTs.

Conclusion

The potential insensitivity of SLE disease activity indices to partial improvements may result in type II errors in SLE RCTs. Varying concomitant pharmacotherapy, especially corticosteroid use, in SLE may blunt observed treatment effects. Steroid tapering should be considered a trial outcome in isolation. More realistic sample size calculations are needed in SLE.

Key words

systemic lupus erythematosus, lupus, rheumatoid arthritis, trial design

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Introduction

Systemic lupus erythematosus (SLE) is heterogeneous affecting several organs with various disease activity. Several randomised controlled trials (RCTs) of biologic therapies in SLE have had marginally successful or negative results. For example, rituximab showed positive results in randomised controlled trials (RCTs) of rheumatoid arthritis (RA) (1-5) and SLE case series (6-8), but trials in SLE failed (9, 10). The failure of rituximab and abatacept (11) could be attributed to inefficacy of the drugs or flaws in the trial design including sample size estimates, outcome measurements, and inclusion and exclusion criteria. Belimumab is the only biologic currently approved for use in SLE (12, 13). Two epratuzumab phase III trials are ongoing (NCT01262365 and NCT01261793). The success of the belimumab trials has been attributed in part to changes in trial design: the development of a new SLE responder index (SRI), the strict control of steroid doses and inclusion criteria requiring seropositivity (positive anti-nuclear antibody [ANA] above a certain cut off). Increases in steroid dose above a certain amount for a certain time frame should be considered treatment non-responders. Trial assumptions of benefit in the population studied will have various designs (head to head with active treatment, failure of stable background immunosuppressive treatment, steroid sparing effect of a drug, and less progression of damage or less flares over time) and/or anti-double-stranded DNA (anti-dsDNA) (14, 15). RA trials use the American College of Rheumatology (ACR) responses and the change in disease activity using the Disease Activity Score (DAS28) *vs.* SLE trials where SRI may be more difficult to obtain than an ACR20.

Two common SLE disease activity measures used historically as endpoints in SLE trials are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI, and modification such as SELENA-SLEDAI and SLEDAI-2K) and the British Isles Lupus Assessment Group (BILAG and BILAG-2004) index. In SLE trials these scales may be very insensitive to modest, yet clinically relevant changes (9, 11-13, 16-19). Valuable data are lost as the scoring systems are present *vs.* absent for many features. Based on results from the phase II belimumab trial (which did not meet primary endpoints) *post-hoc* analyses revealed efficacy in certain subgroups, so a composite SLE disease measure was developed with successful results in belimumab phase III trials (12, 13, 15, 16). The SRI requires a ≥4 point decrease in SELENA-SLEDAI (improvement), no new BILAG A and no more than one new BILAG B score (*i.e.* no major organ worsening although there can be some worsening) and no worsening of the Physician Global Assessment (PGA) (*i.e.* no more than 0.3 point worsening out of 3) (15).

Contrasting RA and SLE RCT designs with respect to inclusion criteria, outcome measures, and concomitant DMARD and steroid use may help improve SLE RCT design. Solutions are suggested with the goal of improving the probability of success in future SLE RCTs.

We had a preconceived idea before studying the literature as the failure of many drugs in SLE has been speculated to be partially due to trial design. For instance, in RA if it were necessary to have 2 or less swollen/tender joints for a drug to be considered successful, there would likely be no biologics on the market; as in any trial, the proportion of patients at trial conclusion with this end point is extremely small and the differences between active treatment and placebo would be extremely underpowered.

Methods

Randomised controlled trials published in RA and SLE were searched from 2005 until July 1, 2013 using PubMed using the key words: 'RA or rheumatoid arthritis', or 'SLE or systemic lupus erythematosus or lupus' and 'randomised' or 'RCT' or 'trial'. Search results were narrowed using the terms 'anti-BLyS,' 'anti-CD20,' 'anti-CD22,' 'anti-TNF alpha', 'abatacept,' 'belimumab,' 'epratuzumab,' 'golimumab,' 'rituximab,' 'tocilizumab,' and 'biologic.' RCTs were including extracting inclusion criteria, sample size es-

timates, outcome measures and results including the proportion that were positive studies comparing RA and SLE trials. Additional trial information was retrieved from ClinicalTrials.gov. Means, standard deviations, ranges and frequencies were calculated.

Results

Twenty-two randomised controlled trials were found in RA (1-5, 20-36) and eight in SLE (9, 11-13, 16, 18, 19). Eleven were excluded as they did not have a biologic (17) or were a review (37) or were not a RCT (7, 8, 10, 31, 38-42). Table I shows the comparison between RA and SLE RCTs. One SLE trial that compared methotrexate to placebo was allowed as several RA trials for comparison had methotrexate as a comparison arm (17). We also analysed the studies without this trial and the results and conclusions were unaltered.

Primary outcome measures

Nineteen of the twenty-two RA trials used the ACR20 measurement as a primary or as a co-primary outcome (17 primary, 2 co-primary), one used the ACR50, four had the Genant modified Sharp score (for progression of Xray damage), and one measured the proportion of patients achieving DAS28 remission (Table I). The baseline DAS28 ±SD (standard deviation) when given ranged from 5.6 to 7.1±0.8 to 1.2.

Of the SLE RCTs examined, the primary outcomes were the BILAG (n=3), the BILAG-based Composite Lupus Assessment (BICLA) (n=1), SLEDAI (n=2), and SRI (n=2) (Table I). The baseline mean SLEDAI scores where provided ±SD ranged from 9.4 to 10.0±3.6 to 5.5 (Table I). Two RCTs reported baseline SLEDAI median scores ranging from 8–14. Baseline BILAG total scores ranged from 14.0 to 14.5±5.1 to 5.6 or medians ranged from 11 to 15.5 calculated with converting letters to numerical ratings (A=9, B=3 and C=1) and totaling the score.

Inclusion criteria

Twelve RA RCTs required participants to have had inadequate responses to methotrexate. Four required inadequate responses to at least one DMARD (especially methotrexate). Five trials required patients to be TNFi failures, 8 excluded patients who had ever taken TNFis. All RA trials required patient to have active, established RA with swollen joint count requirements ranging from 4 to 10 and tender joint count requirements ranging from 4 to 12. Nineteen of 22 RA trials also required elevated CRP or ESR.

Active SLE included at least one BILAG A or two BILAG B scores (five trials), a SLEDAI ≥4 (one), a SLEDAI ≥6 (2 trials) and a SLE Activity Measurement (SLAM-R) score of 8 (one).

Seropositivity

Three RA RCTs required positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibody. The proportion of seropositive (RF or anti-CCP positive) patients ranged from 71–100% in RA trials. Four of eight SLE RCTs, required anti-nuclear antibody (ANA) positivity at screening, two required a history of a positive ANA, and two had no requirements. The proportion of seropositive (ANA or anti-double-stranded DNA [dsDNA] positive) patients in SLE RCTs ranged from 67–100%.

Concomitant steroid and DMARD use

The proportion receiving concomitant corticosteroid treatment in RA RCTs ranged from 39–75% compared to SLE RCTs (49–100%) (Table I). Nineteen of 22 RA trials required the prednisone/prednisolone at 10 mg/day or less and stable throughout the trial; two RA trials did not provide data on corticosteroid use one trial randomised patients to one of three corticosteroid dose regimens (no corticosteroids, IV corticosteroids, or oral and IV corticosteroids) (5). Five RA trials specifically included corticosteroid (oral or injectable) rescue therapy. Several RA trials stipulated that any patient with an increase in steroid dosage above 10 mg/day was counted as a non-responder. RA trials did not allow tapering or changing steroid dosages except in the studies that allowed rescue therapy.

In contrast, all of the eight SLE trials allowed changes in corticosteroid doses. Eight trials allowed tapering with three trials stating steroid tapering as part of the study protocol. Four SLE trials permitted any baseline dosage of corticosteroids less than 100 mg/day, another between 5–40 mg/d, one 5–60 mg/d, one trial cited a protocol-prescribed corticosteroid regimen, and the remaining trial loaded all patients with 30 mg/day steroids for 4 weeks. Eight SLE RCTs allowed investigators to taper steroids at their own discretion, four trials used corticosteroid dose as a secondary outcome. Only ¼ SLE trials stratified randomisation by baseline corticosteroid dosage. A rituximab trial initially loaded everyone with steroids. Two SLE trials stratified patients based on background immunosuppressants. Five SLE RCTs did not stratify randomisation by corticosteroids or immunosuppressants.

Twelve RA RCTs compared active drug to placebo with background failure of methotrexate after a minimum time of use at a minimum to maximum dose Two RA trials also an active arm added to methotrexate placebo. A rituximab trial also varied the steroids with the infusions. Four RA RCTs compared active drug to placebo with background failure of various DMARDs (majority methotrexate). One RA trial after TNFi failure compared golimumab to placebo with optional background DMARD(s) in steady statewhere 29–31% had no background DMARDs (20). Two RA trials were head to head comparisons of tocilizumab and methotrexate in methotrexate unexposed patients (or not recently exposed and could not have been previous methotrexate failures).

All eight SLE RCTs compared active drug to placebo with background immunosuppressants (azathioprine, mycophenolate mofetil or methotrexate) ranging from 42%–100%.

Sample size calculation and expected change in treatment

Table I shows that RA trials were usually larger than SLE trials. Nine of the 22 RA RCTs based their sample size on the expected proportion of ACR20 responses for active and placebo, two RA trials used the difference in radiographic changes and one the difference

Table I. A comparison of RA and SLE randomised controlled trials from 2005 to mid 2013.

	Rheumatoid arthritis	Systemic lupus erythematosus
Number of studies found	22	8
Primary outcome measures used	ACR20 ACR50 Genant modified Sharp score DAS28 (-ESR)	SLEDAI BILAG SRI BICLA SLAM-R
Inclusion criteria	22 with established RA -12 were Methotrexate inadequate responders -5 Post TNFi failure -3 Mtx naïve From 4 to 10 SJC (out of 28) From 4 to 12 TJC (out of 28) 19 required elevated ESR or CRP	4 had 1 BILAG A or 2 BILAG B 1 had SLEDAI ≥4 2 had SLEDAI ≥6
Expected change in treatment	Between groups difference in ACR20 response ranged from 15%–35% Active treatment ACR20 response ranged from 45%–60% Placebo ACR20 response ranged from 25%–40% 30% of the SD difference in Sharp scores 60% reduction in Sharp score from placebo 20% difference in DAS remission rate	Between groups difference in SRI response of 14% Between groups difference in SLAM-R of 3 points 15% reduction in proportion of patients experiencing first flare (a new BILAG A or B) by 52 weeks 25% absolute improvement in the percent change from baseline in SLEDAI in the active group
Mean n + SD (range) per entire trial	542.73 ± 318.29 (172–1250)	375.50 ± 315.38 (86–867)
Mean length of follow-up (weeks) + SD (range)	32.54 ± 13.25 (20–52)	38.5 ± 19.0 (12–52)
Number positive trials (%)	22 (100)	2 (25)
% positive RF/ANA	Range 71–100% RF positive	Range 67–100% ANA positive
Control group (placebo, head to head, standard of care)	14 placebo on background failure of Mtx 100% were on background Mtx (2 also included an arm without background MTX) 1 placebo on background failure of Mtx and varying steroid regimens (added for determining tolerability/ safety of rituximab infusions) 4 placebo on background failure *DMARDs where 100% were on background *DMARDs 1 placebo with optional background **DMARDs 69–71% were one background **DMARDs 2 head to head of active treatment	8 placebo with background failure of standard of care 42 to 100% in the trials were on background Azathioprine, Mycophenylate Mofetil or Methotrexate whereas the remainder were not currently on background immune suppressive therapy beyond steroids
Steroid dose could be adjusted	No Patients required stable prednisone/prednisolone dose ≤10 mg/day (19/22) A dose increase usually meant treatment failure except in studies that allowed a brief pulse of higher dose or a joint injection) only one or two times during the trial and not immediately before an important outcome time point 1 trial compared various dosing of steroids (no steroids, IV, IV and po with the rituximab infusions) which was only at the beginning of the trial	Yes 8/8 studies allowed steroid tapering with 3 stating specific taper goals 4/8 allowed any baseline steroid dose below 100 mg daily prednisone/prednisolone
% on background corticosteroids	Range 39–75	Range 49–100
% using partial or continuous measure of disease activity as a primary outcome measure (ACR20/50/70 or DAS28 or SRI50)	100	0
Baseline mean DAS28 (SD) and mean SELENA-SLEDAI (SD)	5.6–7.1 (0.8–1.2)	9.5–10.0 (3.6–5.5)

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ACR: American College of Rheumatology; DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; SELENA- SLEDAI: safety of estrogens in lupus erythematosus version of the systemic lupus erythematosus disease activity index; BILAG: British Isles Lupus Assessment Group; SRI: Systemic Lupus Erythematosus Responder Index; BICLA: BILAG-based Composite Lupus Assessment; SLAM-R: Systemic Lupus Activity Measurement-revised; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; ANA: anti-nuclear antibody; RF: rheumatoid factor; TNFi: tumour necrosis factor inhibitor; Mtx: methotrexate; DMARD: disease-modifying anti-rheumatic drug *background DMARDs included at least one of methotrexate, chloroquine, hydroxychloroquine, azathioprine, sulfasalazine, parenteral gold or leflunomide. **background DMARDs included at least one of methotrexate, hydroxycholorquine or sulfasalazine (1-5, 9, 11-13, 16-36).

Table II. Lessons from RA that may help with future SLE trial design based on our opinion and the literature where available.

	RA	SLE
Responder Index	A composite measure in RA such as ACR20 needs only 20% improvement in a several measures.	Responder indices in SLE are blunted to minimally clinically important improvements/changes are not detected by most composite scores.
Sample size calculation	Effective biologic treatment in RA at best has 60% obtain an ACR20.	SLE sample sizes may be too optimistic. In general, sample size calculations for mean changes are more sensitive than requiring a proportion of patients to have a marked improvement (no disease activity within an organ) in a composite endpoint.
Background medications	Starting two medications simultaneously is more effective than adding study drug to background failure.	This also applies to increasing or adding background prednisone. This blunts the between groups differences of active *vs.* placebo
Between site differences	There may be geographic differences in response to placebo. This will blunt the treatment effect.	This applies in SLE to steroid use, immune suppressive use, and possibly genetic differences in drug disposition.
Contemporary trials enroll less sick patients than previously	In RA trials, there is less x-ray progression, lower DAS28 at onset than older trials.	This may be true in SLE trials. For instance, lupus neprhitis trials are unlikely to show between groups differences in creatinine over the study period.
Timing of trial is important for the outcome	Remission takes longer to achieve than a change in DAS, ACR 20 occurs more quickly than ACR70.	Proteinuria in lupus nephritis trials may not fully resolve for months or more despite effective treatment; whereas RBC casts will improve more quickly.
Time to outcome may demonstrate treatment differences	X-ray progression and future remission (often in year 2, so beyond RCT timeframe) are affected by time to achieving a large benefit.	Time to a low disease state or time to first response may separate treatment groups and be meaningful re future damage.
Baseline disease activity is important	Patients in high disease activity are more apt to have a large change in DAS but less likely to achieve remission *vs.* if starting in moderate activity, remission is more likely.	SLE patients in high disease at baseline are likely to need more steroids and are less likely to have patients in low disease activity unless the trial is very long (such as SLE DAI<4).
Early *vs.* established disease may yield different results	Early RA has a better chance of remission.	Early SLE has less damage, but the chance of remission may not be different than established disease unless if the latter has more previous treatment failures.
Head to head treatment especially in early disease	In early RA, most patients in a RCT do not need a biologic. Approximately 30% of early RA will obtain remission or a low disease state on Mtx monotherapy or biologic monotherapy. In RA, most biologics are not superior to Mtx in those who have not failed Mtx.	In SLE treated with head to head treatment, it is very difficult to show an advantage of one therapy over another so outcomes may be non0inferiority, time to response or safety. Although there is unmet need in SLE, current immune suppressives are effective in many patients.
Those who have been exposed to multiple previous drugs are more drug resistant in a trial	The effect of biologics in RA is the law of diminishing returns. ACR responses are best in naive, early disease, then Mtx inadequate responders and worst in previous biologics failures. Treatment effect is blunted in those who have failed multiple drugs esp high responses (ACR50, 70, DAS28<2.6).	Sample size calculations should take into account the proportion of subjects enrolled with previous multiple drug failures as these patients are more likely to have a blunted response. Heterogeneity of background drugs increases the standard deviation of response and a larger sample size is needed.
Antibody status	In RA, rituximab has a better response in RF positive patients. This is not necessarily true for all biologics.	ANA negative patients may have a different response to treatment – different pharmacogenomics or even misclassification. New trials have included only ANA positive above a certain level or anti-DNA positive. However, this can affect the generalisability of results to ANA negative SLE patients who are a minority but increasing over time.
Use of steroids	RA trials maintain stable background steroids. To keep a patient in a study a steroid rescue may be needed but not right before a key end point and only a maximum number of times and a maximum dose.	Steroid interventions must be controlled in a trial. If there is a need for a defined dose of steroids the patient could be considered a non-responder if non-adherent to dosing regimen, or the total dose of steroids per patient within each treatment group could be an outcome.
Escape into open label treatment during the study protocol	In RA, if there is an escape arm, more subjects become non-responders.	Studies that allow escape into open label extension with active treatment have more non-responders and more drop outs.
Open label extensions (OLE)	This is a way to keep patients in the RCT and learn more about the safety of a drug in the OLE.	OLE can be used in SLE to enhance recruitment, maintain patients in a study and learn about safety and durability of response after the RCT is completed.

in proportion achieving DAS28 remission. Six RA trials did not report details of sample size calculations. For RA trials that used the ACR20 as the primary endpoint and included data on sample size calculation (11/22), the expected ACR20 response rate in the active treatment was from 45% to 60% and placebo from 25 to 40%; an expected doubling of ACR20 responders comparing active to placebo treatment. One RA trial expected only a 15% difference in response rates between rituximab and placebo in TNFi failures (1). For a head to head trial comparing tocilizumab to methotrexate, methotrexate alone was expected to have a 35% ACR20 compared to 65% for tocilizumab (21). The other tocilizumab head to head trial estimated a 12% difference in ACR20 between methotrexate and tocilizumab (22).

Radiographic scores assumed a difference of 30% of the standard deviation between the placebo and tocilizumab for Xray progression (23). Another study used the Genant modified sharp score with an expected a mean change of 3.7 with placebo compared to a 0.5 with rituximab (3). The abatacept trial expected a 60% reduction in Xray progression using the Sharp score compared to placebo with a progression of 1.27 units (24). One trial expected a between-groups difference DAS remission of 20% between abatacept and placebo (25).

One SLE trial was powered to detect a difference in the SLAM-R, another the SELENA-SLEDAI, two SRI changes, one BILAG, two were said to be underpowered to detect differences epratuzumab and placebo, and one trial did not report the sample size calculation but used BILAG as a primary endpoint. One study anticipated that 60% of patients in the placebo arm would experience a new SLE flare (as assessed by BILAG; new A or B) over 52-weeks with 15% fewer flares with active treatment (11). Another expected a 25% absolute or 100% relative improvement in SELENA-SLEDAI with active treatment assuming a 25% decrease in the placebo group with 65% of the placebo group expected to flare over one year versus 43% with belimumab treatment. These two manuscripts were the only studies (2 of 8) that specified how the placebo group was expected to perform.

Table III. Suggestions of outcomes in SLE trials: points to consider based on our opinion.

Organ specific trials	
Inflammatory arthritis	If arthritis is being studied, the SJC and TJC should be the primary outcome and patients with fibromyalgia may need to be excluded.
Rash	If rash is the being studied, MD and patient global assessment of SLE rash and the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) may be considered as outcomes.
Renal	In renal SLE, head to head comparisons of standard of care *vs.* the new treatment or add on to standard of care can be done with active urinary sediment (red blood cell [RBC] casts, total protein/day) and creatinine as the outcomes as well as time to normalising urinary sediment. WBCs in the urine are not part of lupus nephritis and should not be included as an outcome (unless interstitial nephritis is being studied). Likewise, urinary RBCs may not be due to lupus nephritis. Many patients will do well on standard of care treatment so longer outcomes such as creatiniine, 24hr proteinuria at one and two years may be needed. Time to achieving a certain renal outcome, steroid sparing effect and safety may be the important outcomes.
Flares as an outcome	Flares in SLE patients within trials are frequent and a minimally important flare should be defined as relevant to the drug under study. A flare may need different defintions with a sensitivity analysis – such as MD reported major flare, a major increase in prednisone or a change in SLEDAI by at least 2 or 4 points.
Steroid sparing effects of treatment	A primary outcome could be a steroid sparing effect of a drug where steroids are not strictly mandated in their use and tapering but a suggested protocol of steroid tapering is given and only those with a certain minimum dose of steroids are allowed into the trial.
Head to head trial with active new comparator	The speed of improvement, ability to taper steroids and/or safety may be the primary outcomes or a non-inferiority design.

Discussion

This review is not an exhaustive comparison of all SLE and RA trials. We previously reported that SLE trials were temporally improving in quality (43) and there were many effective RA treatments available before composite indices of ACR and DAS responses were developed. Perhaps studying non-biological treatment over the same time frame would yield further insights. Both SLE and RA trials usually included inadequate responders where either a new treatment or placebo was added. The discussion provides potential solutions either from the observations of the RCTs analysed or from our preconceived ideas or others in the literature. It must be noted that the design of RA trials and outcome measurements used became standardised years before the RA trials were included.

Points to consider

The points we have expressed are opinions and commentary and not necessarily backed by data and may not reflect others including SLE investigators and drug licensing bodies. Table II compares clinical trials in RA and SLE with lessons learned from RA and how that may apply to SLE. Only some points will be discussed in further detail.

Table III illustrates points to consider in SLE trials with suggestions for further SLE studies. It is important to note that another explanation for negative trials are that the drugs studied are not effective in the population studied. Perhaps global assessments should be on a 100 mm VAS to improve sensitivity to change for these measurements. Trial assumptions of benefit in the population studied will have various designs (head to head with active treatment,

Table IV. Trials found for SLE RCTs over the time of the search including whether or not there was success or failure of the primary endpoint(s). Successful trials were far larger.

Wallace, Gordon *et al*. (2013)	failed	Endpoint: BILAG response with no treatment failure at 12 weeks	n=90
Wallace, Kalunian *et al*. (2013)	failed	BICLA (BILAG-2004, SLEDAI-2K, PGA and no treatment failure) at 12 weeks	n=227
J. T. Merrill, Neuwelt *et al*. (2010)	failed	Achieving/maintaining a major clinical response, partial clinical response or no clinical response on BILAG at week 52 (major clinical response=achieving C scores or better in all organs at week 24 without experiencing a severe flare [new A or 2 new B] to week 24 and maintaining this response without a moderate or severe flare [≥1 A or B] to week 52)	n=257 Treatment=169 Placebo=88
J. T. Merrill, Burgos-Vargas *et al*. (2010)	failed	Proportion of patients with with a new SLE flare (BILAG A or B) at any time after initiation of steroid taper	n=175 Treatment=118 Placebo=57
Wallace *et al*. (2009)	failure	% CHANGES SELENA-SLEDAI from baseline to week 24 and time to first mild/moderate or severe flare defined by SFI during 52 weeks	n=449 Placebo=113 Dose 1=114 Dose2=111 Dose 3=111 Total treatment=336
R. Furie *et al*. (2011)	success	SRI response rate at week 52 (≥4 point reduction in SELENA-SLEDAI, no new BILAG A and no more than 1 new B, no worsening [increase ≥0.3] in PGA)	n=819 Placebo=275 Dose 1=271 Dose 2= 273 Total Treatment=544
Navarra *et al*. (2011)	success	Response rate at week 52 assessed with SRI	n=865 Placebo=287 Dose 1=288 Dose 2=290
Fortin *et al*. (2008)	fail	3 point difference in SLAM-R score at 52 weeks	n=86 Placebo=45 Treatment=41

failure of stable background immunosuppressive treatment, steroid sparing effect of a drug, and less progression of damage or less flares over time).

Sample size

Many of the SLE trials had optimistic expectations with respect to improvements and flare rates.

Steroids

We recognise that the use of steroids including dosing is far different in SLE than RA. There is confounding where in most trials the cumulative steroid dose was not a primary outcome measurement so the varying of dosing (both loading and lowering steroids) could have been a major confounder. SLE trials did not require current stable background immunosuppressant treatment not were steroids usually required and if steroids were allowed, far larger doses than that seen in RA trials were included. These are also potential confounders where the effect of an active treatment could be very blunted or modified by steroid use and possibly by the presence or absence of background treatment. Stratified randomisation by immunosuppressant use and steroid use could help resolve some of these confounders as well as not allowing for steroid tapering or having cumulative per person steroid dosage as an outcome measurement would help to reduce bias. If steroid increases are allowed in studies, those who require more steroids (above a certain dose for a certain period of time) could be considered treatment failures in the intent to treat analysis. In SLE a reduction in steroids such as 20% more patients achieving less than 10mg/day of prednisone/prednisolone may be very important if patients with SLE requiring at least 20mg of prednisone are entered into a trial. There could be standardisation of steroid use within SLE trials such as stratification of analyses by those who need to increase steroid dose, use of rescue steroids but continuing study drug and ability to taper steroids in long SLE trials. A consensus should be sought from key opinion leaders and drug licensing bodies.

Responder indices

Responder indices in SLE RCTs are insensitive to modest changes, and the results do not always correlate well with the clinical picture. These tools cannot detect minimal clinically relevant improvements. Although SLEDAI and BILAG have both been validated to detect changes in disease activity, they were designed to follow cohorts. SLEDAI measures some disease activity items on an "all or none" basis. Either a disease manifestation is present or it is absent or low. Whereas, in RA ACR20, 50, and 70 scores combine

measures of disease activity into one score but specifically measure levels of partial improvement (44). The proportion of patients achieving an ACR20 is the primary outcome in many RA trials. ACR50 and ACR70 are usually secondary outcomes. For biologics in RA, at most 2/3 have a 20% improvement (in the ACR20) (21). In a RCT, a patient with RA who started the trial with 20 swollen joints but who experienced at least a 20% decrease in swollen and tender joints (thus having at most 16 joints still involved) and had 20% improvement in the MD and patient global scores, the ESR and the HAQ (Health Assessment Questionnaire Disability Index) score would be considered a success; but if a lupus patient in a SLE trial felt the same effects she would be considered a treatment failure because SLEDAI would not improve until less than or equal to two joints were involved before the score can change for the arthritis component of the SLEDAI.

The SRI lacks the ability to detect partial improvements in SLE manifestations as some areas of the BILAG and SLEDAI count a manifestation as either present or absent without considering a continuous range of improvement within many organs or a partial percentage improvement.

In the SLEDAI, 50% improvement from baseline in rash, swollen joint count and anti-DNA titre would not be regarded as improvement if the rash was still present, the swollen joint count was still more than 2 and the anti-DNA titre was still positive. However, both the patient and the physician may determine there is clinically relevant improvement but this is contradictory to the unchanged SLEDAI score. This inconsistency is reflected in trials in which the primary outcome as measured by a decrease in SLEDAI score is not achieved but the Physician's Global Assessment (PGA) and SF-36 physical component score (PCS) show significant improvements. In a phase II RCT assessing the efficacy of abatacept in SLE, the primary outcome as measured by the proportion of patients with any new flare (BILAG A or B) at any time after steroid taper was not met; but the PCS of the SF-36, fatigue and sleep problem scores were significantly better in the abatacept group and the number of physician-assessed flares was lower than the number of flares determined by the BILAG in the abatacept group (11, 16). The PGA is included in the SRI but is only required not to worsen. However if the PGA is markedly improved, the patient is a non-responder if the SLEDAI does not improve by at ≥4 points. Also, the PGA scale is from 0 to 3, whereas in RA trials it is usually scored from 0 to 10 or 0 to 100 (using a 100 mm VAS). The minimal clinically important difference for global assessments in RA and SLE are small, and these differences could be missed on a scale that is compressed from 0 to 3 (45-47).

If the emergence of any one new BILAG B score is used as an endpoint, patients could be considered treatment failures even though a physician wouldn't have considered the flare as relevant. In the rituximab SLE trial entering with active non-renal and non-CNS SLE, the primary outcome required patients to achieve a major or partial clinical response (9); defined as achieving all BILAG C scores or better in all organs without experiencing a severe flare (a new A score or two new B scores on BILAG) at week 24 and maintaining this response to week 52 without a moderate or severe flare (≥1 new A or B BILAG scores). The expected benefits of active treatment were likely overly optimistic due to the fluctuations in SLE BILAG B scores (half of which may not be considered flares relevant to intensifying treatment by the physician evaluator). The SRI composite score uses BILAG to ensure that any improvement in SLEDAI is not accompanied by worsening in other organs. A new BILAG A or more than one new BILAG B would result in a negative SRI response. The SRI may suffer similar problems with respect to BILAG B flares that may not be clinically relevant.

Many clinicians consider increases in SLE treatment when the patient has active organ involvement, not solely when the serology is active; so perhaps having anti-DNA and complements in a disease activity measure may not be an outcome of clinical importance. In RA, the goal is not to convert a patient to seronegative in their RF or CCP; whereas an elevated CRP in active RA is associated with an increased chance of joint erosions so treatment goals may include reduction in the swollen and tender joint counts, pain, global assessments of RA and inflammatory markers. In SLE, there is less chance to respond with a SLEDAI if anti-DNA is negative and complements are normal. However, there have been successful end points in SLE such as the composite end point (SRI) and in secondary analyses a change in SLEDAI if damage was low as measured by the SLICC SDI and steroid sparing effects (Table IV). Successful trials were far larger.

Juvenile-onset systemic lupus erythematosus (jSLE) uses a separate measure of disease activity (48, 49). The Paediatric International Rheumatology Trials Organisation (PRINTO)/ACR provisional response criteria index (PCI) bases improvement on the five jSLE core response variables: physician's global assessment of disease activity, parents' or patient's global assessment of patient wellbeing, SLEDAI, 24 hour proteinuria, and health-related quality of life (49, 50). The PCI defines improvement as clinically relevant when there is at least 50% improvement in at least two of the five core response variables with no more than one of the remaining variable worsening by more than 30% (50). In a study comparing the performance of the SRI and the PCI in jSLE, it was found that the PCI had greater accuracy in detecting major improvements than the SRI (51).

The lack of assessment tools for partial improvement in disease activity was recognised and the SLEDAI Responder Index 50 (SRI-50) was designed and tested for validity (52, 53); where 50% improvements for each item in SLEDAI-2K. The SRI-50 has not been used in any SLE RCT but reflected more improvement than the SRI (52). Another study found that using the SRI-50 in place of the SLEDAI-2K in the SRI significantly increased the percentage of participants who qualified as responders to traditional DMARDs from 29%–35%, reflecting the ability of the

SRI-50 to reflect partial improvements in disease activity (53).

Perhaps a composite scoring system is not the best way to evaluate improvement in SLE. Lupus can affect each organ system differently, with variable severity and potential reversibility and at different times. Disease activity measures such as SLEDAI and BILAG give separate scores for different manifestations but combine these scores into an overall index of disease activity. Treatment may not be as effective in one organ domain as it is in another. A drug that significantly reduces a rash may not have any effect on glomerulonephritis. SLE trials could focus on subgroups of specific manifestations and evaluate drugs separately for each manifestation (54). For example, if a particular medication is effective in the musculoskeletal system but has minor or insignificant effects in the mucocutaneous and other systems, testing the drug in a patient population with mixed lupus manifestations, the effects in certain domains may be obscured by the inefficacy in patients that do not exhibit the symptoms that the drug is most efficacious for. One way to control for the heterogeneity of SLE would be to stratify patients based on specific manifestations or include only patients with the organ of interest that is active. This is the case for lupus nephritis trials and a recently completed negative trial of SLE with inflammatory arthritis with laquinimod (NCT01085084). Other outcomes could be the time to achieving a certain end point such as the time to reducing proteinuria by 50% if only those with active glomulonephritis are enrolled in a trial. Fully clearing an active urinary sediment and all proteinuria will take longer than the trial time for many patients. The kinetics of response for various organs need to be taken into consideration in trial design.

A study by Favalli *et al*. demonstrated that period of study enrolment and publication year are inversely correlated with results in RA RCTs (55), finding more recent publications gives less positive results possibly due to the increase in heterogeneity after phase II trials and the notion that the effects of drugs are usually larger earlier in drug development.

Conclusion

In future SLE trials, randomisation can be stratified by region, ethnicity, stable background immunosuppressant, steroid use, and major organ involvement. There is a need to consider alternate outcome measurements in SLE trials that are more responsive to minimal but important change and account for steroid use by stratification, protocol and/or as an outcome. Novel modifications in trial design may help to balance the heterogeneity in SLE between treatment groups (stratification at time of randomisation) and lessen Type II errors.

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