Systematic Review and the External Validity of Randomized Controlled Trials in Lupus Nephritis

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Introduction: Randomized controlled trials (RCTs) are considered the gold standard for assessing treatment efficacy. However, sampling bias can affect the generalization of results to routine clinical practice. Here we assessed whether patients with lupus nephritis (LN) seen in routine clinical practice would have satisfied entry criteria to the major published RCTs in LN.

Methods: A systematic literature search from January 1974 to May 2015 was carried out, identifying all RCTs investigating LN induction treatment. Patients diagnosed with proliferative or membranous LN between 1995 and 2013 were identified from the Barts Lupus Centre database; baseline characteristics were compared with each RCT's entry criteria to assess hypothetical inclusion or exclusion.

Results: Of 363 articles, 33 RCTs met inclusion criteria. Of 137 patients newly diagnosed with LN (111 with proliferative/mixed proliferative and 26 with pure membranous LN), 32% would have been excluded from RCT entry (range 8%–73%). The main reasons for exclusion would have been too severe disease, too mild disease, or prior immunosuppressant use, which were exclusion criteria in 26, 20, and 22 RCTs, respectively. A total of 27 patients with LN (20%) were re-biopsied due to flare; 68% of these would have been ineligible to enter RCTs.

Conclusion: Published RCTs do not truly reflect the heterogeneity of patients with LN in routine practice at our lupus center. The external validity of RCTs could be improved by including more representative patient cohorts. RCTs should be used as a guide but consideration should be given to similarities between individual patients and the characteristics of the trial cohorts before treatment decisions being made.

Tremendous advances in immunosuppressive treatment of lupus nephritis (LN) have been made over the past 4 decades. Fortunately, most treatment decisions made in routine clinical practice are now based on results from well-designed clinical trials rather than anecdotal evidence. Randomized controlled trials (RCTs) are considered the "gold standard" to assess treatment efficacy,[1,2] as they have the best potential to minimize bias through allocating participants to study arms in a random fashion. Despite their rigorous design, the applicability of results to individual patients has been debated thanks to other types of bias, some of which lead to RCTs not adequately reflecting the heterogeneity of patients in routine clinical practice.[3] Examples include "selection bias" due to poor allocation concealment, "sampling bias" when physicians consider only a certain type of patient for trials and exclude patients on the basis of the lack of personal equipoise, or "literacy bias" for those who fail to understand the consent form.[4]

In LN RCTs, a particular problem may be "severity of illness bias."[4] To achieve a more homogeneous study population in whom the study drug is most likely to work and less likely to harm, patients must meet a range of prespecified entry requirements.[5] Inclusion criteria to LN RCTs often specify the target range of biochemical variables and serological activity markers, and the histological evidence of LN with restriction to 1 or 2 particular classes of glomerulonephritis. Moreover, exclusion criteria intentionally eliminate patients with mild or, more commonly, severe disease; those with

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recent major infections or with preexisting comorbidities; and tend to prohibit certain immunosuppressive drugs before enrollment. As a consequence, patients recruited to most LN RCTs have a relatively moderate disease activity excluding those with too mild or severe disease and those developing active LN while on immunosuppressive therapies.

In this study, we aimed to evaluate the external validity of published LN RCTs. We assessed whether a multiethnic cohort of patients with lupus seen in routine clinical practice at a single center would have been represented adequately by assessing RCT inclusion and exclusion criteria.

METHODS

Patients and Study Design
This study was conducted at Barts Health NHS Trust, the largest tertiary teaching hospital in the United Kingdom. Patients with biopsy-proven proliferative (class III or IV) or membranous (class V) LN diagnosed between 1995 and 2013 were included. LN classes based on glomerular pathology were defined according to the International Society of Nephrology/Renal Pathology Society 2003 classification.[6,7] All patients fulfilled at least 4 of the American College of Rheumatology revised classification criteria for systemic lupus erythematosus.[8] Clinical data were collected retrospectively from electronic patient records; baseline variables included serum creatinine, glomerular filtration rate (GFR), serum albumin, proteinuria, double-stranded DNA, and complement C3 and C4 levels. Baseline immunosuppressive drugs at time of LN onset were recorded.

Identification of Eligible Clinical Studies
We selected RCTs that aimed to measure the efficacy of immunosuppressive agents in proliferative (class III, IV) and/or membranous (class V) LN induction treatment. Literature searches were performed using PubMed, Medline, and EMBASE databases (from 1974 to May 2015) and the Cochrane Controlled Trial Register (up to May 2015) using the OVID search engine, to identify relevant studies. Key search words included "lupus nephritis" and "randomized" and "lupus nephritis" and "clinical trial." Additional studies were sought through bibliographic notations. Studies published in full-text English literature were included if they met the following criteria: (i) prospective controlled trial with treatment allocation by random assignment; (ii) compared at least 2 arms for LN induction treatment; (iii) involved proliferative and/or membranous LN patient population; and (iv) included adult patients. We excluded trials that published data

on extended follow-up of already published RCTs, studies of maintenance therapies, or refractory LN.

Evaluation of Hypothetical Noninclusion Rate to RCTs
Baseline characteristics of patients in the Barts LN cohort were compared with patients participating in some of the most important RCTs of LN induction treatment from the past 2 decades.

For the purpose of this study, factors leading to exclusion included severe renal impairment with predefined GFR or serum creatinine in the selection criteria of the RCT; mild disease with predefined levels of proteinuria, serum albumin, GFR, or serum creatinine; or prohibited baseline immunosuppressive drugs used at time of LN onset. We did not analyze any other exclusion criteria, including confounding factors not related to their renal disease.

When trials involved patients with proliferative glomerulonephritis (class III or IV ± V), we evaluated only the patients with proliferative LN from our cohort ($n = 111$); where trials recruited patients with membranous LN, we evaluated only our membranous LN cohort ($n = 26$), whereas our entire cohort was compared ($n = 137$) when both classes were represented in the RCT.

RESULTS

Characteristics of RCTs Included in the Analysis
Our systematic literature search yielded 363 articles, of which 309 articles were deemed unsuitable after title or abstract review (Figure 1). Of the remaining, 5 trials on LN induction treatment had to be excluded, as the study design was insufficiently described and no comment was made on inclusion and exclusion criteria used. The final analysis composed of 33 RCTs is shown in Table 1.[9–41]

Of the 33 RCTs, 19 journal articles (58%) failed to report the methods of randomization and/or the protocols used to assign participants to comparison groups. Furthermore, only 4 RCTs[27,31,39,40] published the rate of screening failure, ranging from 19.6% to 39.4%. There were only 2 of 33 RCTs elaborating the reasons for ineligibility.[27,31]

The most frequently prespecified inclusion and exclusion criteria encountered in the selected RCTs are detailed in Table 2. Nearly all RCTs (97%) required fulfillment of systemic lupus erythematosus classification criteria, but a positive antinuclear antibody/lupus erythematosus test was rarely desired (18%). Three trials (9%) did not require biopsy evidence of LN; 75% of RCTs required patients to have a renal function that met predefined values, and 67% of studies demanded a
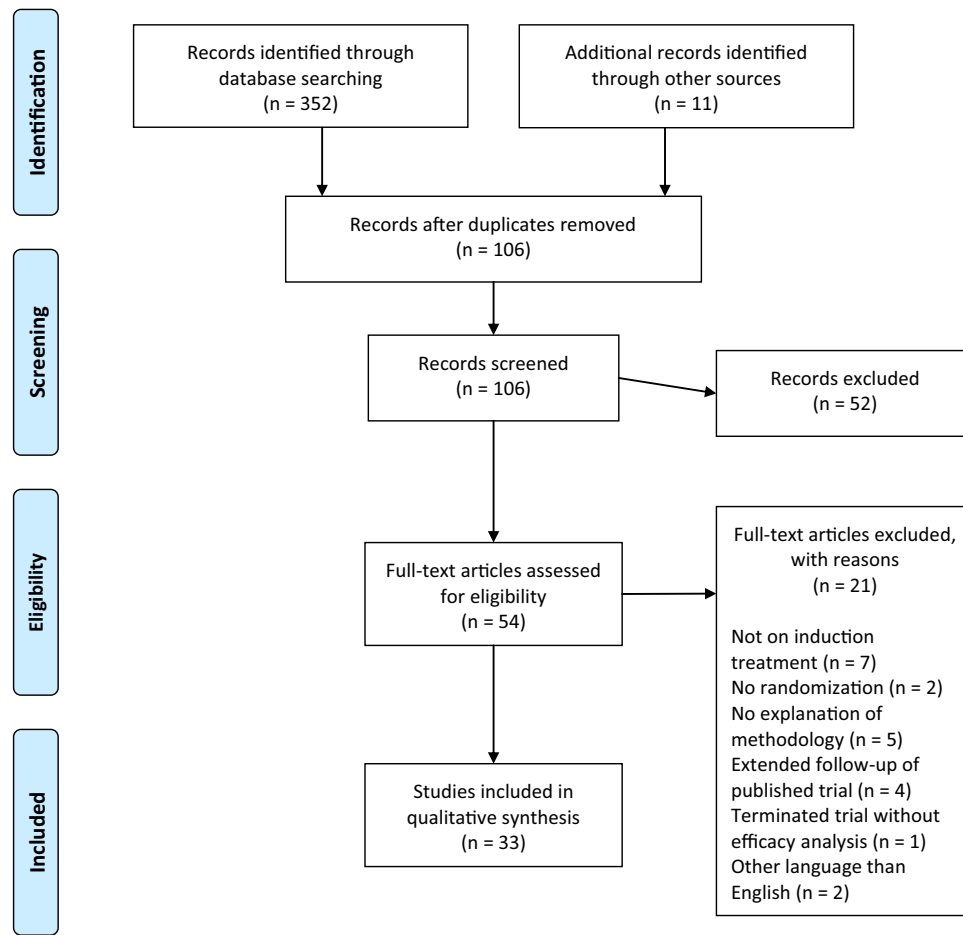
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

minimal level proteinuria. Prohibited concomitant or prior immunosuppressive treatment was defined in 76% of RCTs.

Characteristics of Barts LN Patient Cohort

From our database, we identified 137 patients with a new diagnosis of biopsy-proven active LN; their baseline characteristics are shown in Table 3. Eighty-one percent of our LN cohort had proliferative ($n = 111$, 30% class III, 51% class IV, with or without membranous component), and 19% had pure membranous LN ($n = 26$). Overall, patients with LN in our cohort tended to have more severe renal disease compared with patients in landmark RCTs of LN induction (Table 4)[42]; they had a mean proteinuria of 5.5 g/24 h ($\pm$ 5.1 SD), mean serum albumin of 27.3 g/l ($\pm$7.4 SD), and mean serum creatinine of 159 μmol/l ($\pm$ 166 SD). Although 33% ($n = 45$) had a normal GFR (>90 ml/min per 1.73 m^2), 18% ($n = 25$) had a GFR <30 ml/min per 1.73 m^2. Serological evidence of lupus activity was present in half of the cohort with strongly positive double-stranded DNA and low complements. Twenty-three patients with systemic lupus

erythematosus (16.7%) were taking immunosuppressants other than hydroxychloroquine or oral prednisolone (either mycophenolate mofetil or azathioprine) at time of LN diagnosis.

Hypothetical Noninclusion Rate of Newly Diagnosed Patients With LN to LN Induction RCTs

On average, one-third (31.8%) of our newly diagnosed biopsy-proven active LN cohort would have been ineligible to enter the RCTs (range 8.1%–72.9%) (Figure 2). These patients would have been excluded because of factors directly related to their renal disease or the concomitant use of immunosuppressive treatment. Severe renal impairment was a prespecified exclusion criterion in 26 RCTs (79%) leading to ineligibility in up to 61.4% of our LN cohort. Twenty RCTs (63%) would have left out patients with milder disease based on mildly impaired renal function or lower level of proteinuria, resulting in a hypothetical exclusion rate reaching up to 44.1%. Additionally, 22 RCTs (67%) prohibited the use of various immunosuppressive drugs resulting in exclusion rates of 16.1% of our LN cohort.

Table 1. An overview of 33 randomized controlled trials of lupus nephritis induction treatments published since 1970

Author, Year	Study design	Follow-up	n	LN classes	Treatment arms
Steinberg AD et al.[9] 1971	Double-blind single center (USA)	10 wk	13	Biopsy not required	G1: p.o. CYC G2: placebo
Steinberg and Decker[10] 1974	Double-blind single center (USA)	10 wk	38	Diffuse proliferative (IV)	G1: p.o. CYC G2: AZA G3: placebo
Ginzler E et al.[11] 1976	Double-blind single center (USA)	12 mo	14	Diffuse proliferative (IV) or membranous (V)	G1: AZA G2: p.o. CYC + AZA
Donadio JV et al.[12] 1978	Open label single center (USA)	Mean 43 mo	50	Diffuse proliferative (IV)	G1: p.o. CYC + p.o. corticosteroid G2: p.o. corticosteroid
Dinant H et al.[13] 1982	Open label single center (USA)	Mean 42 mo	46	Biopsy not required	G1: p.o. corticosteroid G2: p.o. CYC + AZA G3: i.v. CYC
Boumpas DT et al.[14] 1992	Open label single center (USA)	30 mo	65	Proliferative (III or IV) or membranous (V)	G1: i.v. corticosteroid G2: short course i.v. CYC G3: long course i.v. CYC
Lewis EJ et al.[15] 1992	Open label multicenter (USA)	Mean 136 wk	86	Proliferative (III or IV)	G1: p.o. corticosteroid + p.o. CYC G2: p.o. corticosteroid + p.o. CYC + PE
Doria A et al.[16] 1994	Open label single center (Italy)	Mean 23 mo	18	Diffuse proliferative (IV)	G1: AZA G2: AZA + PE
Sesso R et al.[17] 1994	Open label single center (Brazil)	Mean 15 mo	29	Biopsy not required	G1: i.v. CYC G2: i.v. corticosteroid
Gouerly MF et al.[18] 1996	Open label single center (USA)	Minimum 5 yr	82	Proliferative (III or IV)	G1: i.v. CYC G2: i.v. corticosteroid G3: i.v. CYC + i.v. corticosteroid
Wallace DJ et al.[19] 1998	Open label international	24 mo	19	Proliferative (III or IV)	G1: i.v. CYC G2: i.v. CYC + PE
Chan TM et al.[20] 2000	Open label single center (Hong Kong)	12 mo	42	Diffuse proliferative (IV)	G1: MMF G2: p.o. CYC
Houssiau FA et al.[21] 2002	Open label international (Europe)	Median 41 mo	90	Proliferative (III or IV)	G1: high dose i.v. CYC G2: low dose i.v. CYC
Yee CS et al.[22] 2004	Open label international (Europe)	Mean 3.5 yr	32	Proliferative (III or IV)	G1: i.v. CYC G2: p.o. CYC
Ong LM et al.[23] 2005	Open label national (Malaysia)	6 mo	54	Proliferative (III or IV)	G1: MMF G2: i.v. CYC
Ginzler EM et al.[24] 2005	Open label national (USA)	24 wk	140	Proliferative (III or IV) or membranous (V)	G1: MMF G2: i.v. CYC
Grootscholten C et al.[25] 2006	Open label national (Netherlands)	Median 5.7 yr	87	Proliferative (III or IV)	G1: i.v. CYC G2: AZA + i.v. corticosteroid
Bao H et al.[26] 2008	Open label single center (China)	9 mo	40	Diffuse proliferative and membranous (IV + V)	G1: MMF + Tac G2: i.v. CYC
Appel GB et al.[27] 2009	Open label international	24 wk	370	Proliferative (III or IV) or membranous (V)	G1: MMF G2: i.v. CYC
Austin HA et al.[28] 2009	Open label single center (USA)	12 mo	42	Membranous (V)	G1: p.o. corticosteroid G2: i.v. CYC G3: CsA
Li EK et al.[29] 2009	Open label single center (Hong Kong)	48 wk	19	Proliferative (III or IV)	G1: RTX G2: RTX + i.v. CYC
Sabry A et al.[30] 2009	Open label single center (Egypt)	12 mo	46	Diffuse proliferative (IV)	G1: high dose i.v. CYC G2: low dose i.v. CYC
El-Shafey EM et al.[31] 2010	Open label single center (Egypt)	24 wk	47	Proliferative (III or IV)	G1: MMF G2: i.v. CYC
Zavada J et al.[32] 2010	Open label, international (Czech Republic, Slovakia)	18 mo	40	Proliferative (III or IV)	G1: i.v. CYC G2: CsA
Chen W et al.[33] 2011	Open label national (China)	6 mo	81	Proliferative (III or IV) or membranous (V)	G1: Tac G2: i.v. CYC
Li X et al.[34] 2011	Open label single center (China)	24 wk	62	Proliferative (III or IV) or membranous (V)	G1: MMF G2: Tac G3: i.v. CYC
Rovin BH et al.[35] 2012	Double-blind, international (USA, Latin-America)	52 wk	144	Proliferative (III or IV)	G1: MMF G2: MMF + RTX
Yap DY et al.[36] 2012	Open label national (China)	24 mo	16	Membranous (V)	G1: MMF G2: Tac
Mysler EF et al.[37] 2013	Double-blind international	48 wk	381	Proliferative (III or IV)	G1: MMF or i.v. CYC G2: low dose OCR + MMF or i.v. CYC G3: high dose OCR + MMF or i.v. CYC

Table 1. (Continued)

Author, Year	Study design	Follow-up	n	LN classes	Treatment arms
The ACCESS Trial group[38] 2014	Double-blind international (USA, Mexico)	52 wk	137	Proliferative (III or IV)	G1: ABT + i.v. CYC G2: i.v. CYC
Furie R et al.[39] 2014	Double-blind, international	52 wk	300	Proliferative (III or IV)	G1: MMF G2: low dose ABT + MMF G3: high dose ABT + MMF
Liu Z et al.[40] 2014	Open label national (China)	24 wk	544	Proliferative (III or IV) or membranous (V)	G1: Tac + MMF G2: i.v. CYC
Mok CC et al.[41] 2014	Open label national (Hong Kong)	6 mo	150	Proliferative (III or IV) or membranous (V)	G1: MMF G2: Tac

ABT, abatacept; AZA, azathioprine; CsA, cyclosporin; CYC, cyclophosphamide; G, group; LN, lupus nephritis; MMF, mycophenolate mofetil; n, number of patients; OCR, ocrelizumab; PE, plasmapheresis; RTX, rituximab; Tac, Tacrolimus.

Hypothetical Noninclusion Rate of Relapsed Patients With LN to LN Induction RCTs

Next, we analyzed hypothetical exclusion rates of relapsed patients with LN with active LN evidenced by a repeat kidney biopsy. Twenty-nine of 137 patients with LN (21.2%) had a repeat kidney biopsy. The median time to repeat biopsy was 28 months (interquartile range 13–47 months). Of those, 27 had active LN, 24 proliferative (class III or IV with or without class V, 88.9%), and 3 pure membranous (class V, 11.1%). Two patients had end-stage LN (class VI, 7.4%) and because indication for repeat biopsy was persistent disease activity rather than flare, they therefore were excluded from the following analysis.

We found that due to strict trial designs, on average, 67.7% of patients with LN with renal flares would have been ineligible to participate in these RCTs (range 7.4%–100%). Severe disease excluded up to 63.2% of the repeat biopsy cohort (average 19.2%), and mild

Table 2. Commonly used eligibility and exclusion criteria of the 33 RCTs

Eligibility criteria	n (%)
Fulfillment of systemic lupus erythematosus criteria according to ARA or American College of Rheumatology	32 (97.0)
Predefined serum creatinine or glomerular filtration rate	25 (75.8)
Predefined minimal proteinuria	22 (66.7)
Age limitation	19 (57.6)
Active urinary sediment	12 (36.4)
Predefined histopathological changes (other than class)	10 (30.3)
Positive antinuclear antibody/lupus erythematosus test	6 (18.2)
Abnormal lupus activity markers, double-stranded DNA, complements	4 (12.1)
Exclusion criteria	**n (%)**
Prohibited immunosuppressive medication	25 (75.8)
Pregnancy	24 (72.7)
Major infection	22 (66.7)
Malignancy	11 (33.3)
Cytopenia	11 (33.3)
Hypersensitivity to a study drug	10 (30.3)
Diabetes	10 (30.3)
Gastrointestinal hemorrhage, peptic ulcer disease	8 (24.2)
Liver disease	7 (21.2)
Cerebral lupus	6 (18.2)
Nonlupus renal disease	5 (15.2)
Unwilling to use contraception	5 (15.2)
Anticipation of poor compliance	4 (12.1)

ARA, American Rheumatism Association; RCT, randomized controlled trial.

Table 3. Baseline characteristics of our LN cohort

Characteristic	Barts LN cohort, n = 137
Gender, n (%)	
Male	20 (15.6)
Female	117 (85.4)
Ethnicity, n (%)	
White Caucasian	22 (16.1)
Black	69 (50.4)
Asian[a]	46 (33.5)
Age, yr, mean (SD)	
at SLE diagnosis	30.8 (11.3)
at LN diagnosis	33.6 (11.5)
Serology, n (%)	
ANA positive	131 (97.0)
ENA antibody positive	97 (75.8)
RNP antibody positive	57 (44.5)
Sm antibody positive	40 (31.3)
Ro antibody positive	54 (42.2)
aPL antibodies	30 (25.4)
Renal histology class, n (%)	
Class III LN (± class V)	41 (30.0)
Class IV LN (± class V)	70 (51.1)
Class V LN	26 (19.0)
Biochemical variables, mean ± SD	
Proteinuria (g/24 h)	5.5 ± 5.1
Serum albumin (g/l)	27.3 ± 7.4
Serum creatinine (μmol/l)	159.2 ± 166.1
Range of GFR (ml/min per 1.73 m^2), n (%)	
≥90	45 (32.8)
≥60 to <90	31 (22.6)
≥30 to <60	36 (26.3)
≥15 to <30	11 (8.0)
<15	14 (10.2)
Lupus activity markers, n (%)	
Range of anti-dsDNA titer, IU/ml	
<30 (negative)	37 (30.1)
30 to 60 (low positive)	14 (11.4)
60 to 200 (positive)	15 (12.2)
>200 (strong positive)	57 (46.3)
Low complement C3	78 (68.4)
Low complement C4	82 (69.5)

ANA, antinuclear antibody; aPL, antiphospholipid; dsDNA, double-stranded DNA; ENA, extractable nuclear antigens; GFR, glomerular filtration rate; LN, lupus nephritis; n, number of patients; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; Sm, Smith.
[a]South Asians (n = 39) and Oriental Asians (n = 7).

Table 4. Overview of patient cohorts in important RCTs of LN induction

Characteristic	Barts cohort	Gouerly MF et al.[18] 1996	Chan TM et al.[20] 2000	Houssiau FA et al.[21] 2002	Ginzler EM et al.[24] 2005	Appel GB et al.[27] 2009	Rovin BH et al.[35] 2012	Furie et al.[39] 2014
Gender, *n* (%)								
Male	20 (15.6)	14 (16.7)	3 (7.1)	6 (7.0)	14 (10.0)	57 (15.4)	14 (9.7)	47 (15.8)
Female	117 (85.4)	68 (82.9)	39 (92.9)	84 (93.0)	126 (90.0)	313 (84.6)	130 (90.3)	251 (84.2)
Ethnicity, *n* (%)								
White Caucasian	22 (16.1)	57 (69.5)	0	76 (84.4)	24 (17.1)	147 (39.7)	45 (31.3)	111 (37.2)
Black	69 (50.4)	18 (22.0)	0	8 (8.9)	79 (56.4)	46 (12.4)	40 (27.8)	14 (4.7)
Asian	46 (33.5)	2 (2.4)	42 (100)	6 (7)	8 (5.7)	123 (33.2)	7 (4.9)	164 (55.0)
Renal histology class, *n* (%)								
Class III LN (± V)	41 (30.0)	62 (78.5)	0	21 (23.3)	NK	58 (15.7)	49 (34.0)	78 (26.2)
Class IV LN (± V)	70 (51.1)	17 (21.5)	42 (100)	62 (68.9)	NK	252 (68.1)	95 (66.0)	220 (73.8)
Class V LN	26 (19.0)	0	0	7 (7.8)	39 (27.9)	60 (16.2)	0	0
Biochemical variables, mean ± SD								
Proteinuria (g/24 h)	5.5 ± 5.1	4.0 ± 0.7[a]	4.8 ± 3.2[b]	3.04 ± 2.4	4.2 ± 2.4[b]	4.1 ± 3.7	4.0 ± 2.9	4.4 ± 5.5[b]
Serum albumin (g/l)	27.3 ± 7.4	NK	28.0 ± 5.5[b]	30.3 ± 6.1	27.5 ± 7.6[b]	NK	26.5 ± 7.5[b]	NK
Serum creatinine (μmol/l)	159.2 ± 166.1	102.0 ± 9.9[a]	106.1 ± 39.8[b]	101.7 ± 58.3	94.6 ± 45.1[b]	101.0 ± 1.1	88.4 ± 44.2	73.6 (35–239)[c]

LN, lupus nephritis; *n*, number of patients; NK, not known.
[a]Combined mean ± SE.
[b]Combined mean ± SD.
[c]Combined median (range).

disease caused ineligibility rates up to 51.9% (average 12.9%). Overall, 57.5% of patients would have been prevented from entering the 33 RCTs because of prior use of immunosuppressive agents, with 11 RCTs (33.3%) excluding more than 80% of our cohort.

DISCUSSION

Current standard of care in LN induction remains suboptimal and kidney damage occurs despite using the best available therapies. The rationale behind choosing one immunosuppressive drug over another or in combination is based on knowledge gained from trials conducted in the past 5 decades. Among those, explanatory RCTs are most valuable, but can be susceptible to bias, using narrow inclusion and exclusion criteria to recruit those most likely to benefit from a drug and least likely to experience harm.[4,5]

RCTs must not only be internally valid but clinically useful and relevant to lupus patient populations. The present study is the first to evaluate eligibility of patients with LN seen in everyday practice for inclusion into published RCTs. Our results indicate that LN RCT populations may only partially reflect real-world LN cohorts and caution should be exercised in extrapolating trial data to patient subgroups that have not been adequately represented in studies. Overall, 32% of our LN cohort would have been excluded from the reviewed 33 RCTs because of the severity of their renal disease and/or the use of an immunosuppressive drug at the time of diagnosis. Eligibility criteria and hence exclusion rates showed a wide range of variability among the examined trials, and reached up to 61% due to severe disease (low GFR or high serum

creatinine), up to 44% due to mild disease (low-level proteinuria or preserved renal function), and up to 16% due to concomitant immunosuppressive drugs at time of LN onset. These findings suggest that RCT results are less likely to be relevant to patients with severe LN who would have never made it to the trial. Exclusion rates were even higher, on average 68%, when examining our existing LN population, with new renal flares having had a repeat kidney biopsy proving active LN. This further queries the application of RCT results to patients with severe LN and those who are nonresponders to other immunosuppressive treatments.

In this study, we focused only on exclusion criteria directly related to LN: disease severity and immunosuppressive status at time of LN diagnosis. There are other factors listed in trial designs that would have further increased exclusion rates if examined. The most important ones are previous immunosuppression, pregnancy, and medical conditions associated with safety of study subjects: infections, malignancy, and comorbidities, such as cytopenia, diabetes, peptic ulcer disease, and cerebral lupus. Some of these criteria further weaken the representation of a real-life LN population; nevertheless, there is no solution that could address the problem without jeopardizing patient safety. However, implementing less conservative exclusion criteria, particularly with regard to comorbidities, in late-stage clinical trials might improve the generalizability.

Stringent eligibility criteria are likely to limit the external validity of RCTs; nevertheless, clinicians should be able to use their judgment when interpreting the results of published trials. Having said that,
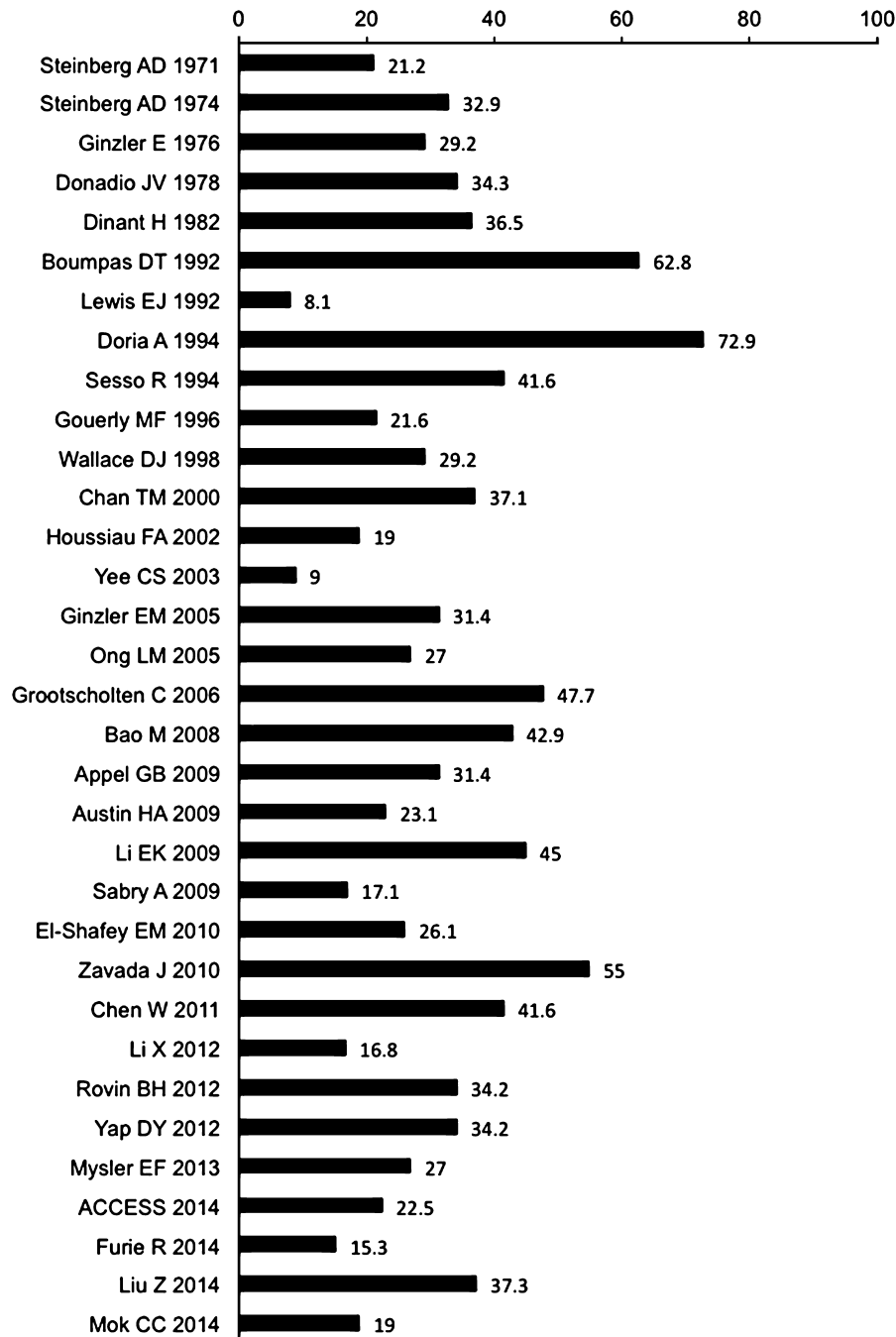
Figure 2. Noninclusion rates to landmark lupus nephritis (LN) randomized controlled trials (RCTs). The proportion of our patients with LN that would not have been included in RCTs is shown. Overall on average 32% of our patients with LN would not have been eligible to participate in the RCTs listed (range 8%–73%).

inadequate reporting of trials can often mislead decision making in prescribing practice. We found a large variation in the quality of reporting of LN RCTs. None of the RCTs published the "screening rate," the number of patients who were diagnosed with LN and assessed for eligibility using inclusion/exclusion criteria. What is more disappointing is that only 4 of the 33 RCTs published "ineligibility rates," and only 2 published the factors leading to nonparticipation. In one of the most cited and influential LN articles, in the Aspreva Lupus Management Study (ALMS) cohort,

13% of screened patients with LN did not meet entry criteria due to mild clinical activity or prohibited concurrent medications.[30] In our cohort, the hypothetical rate of exclusion from the ALMS trial for these reasons would have reached 29%, despite that our LN cohort seemed to have a more severe disease compared with ALMS study subjects. An explanation for the discrepancy could be the ethnic background of the participating subjects, with a higher proportion of white patients (40%) in the ALMS versus our cohort (16%), and the low proportion of black patients

(12% vs. 50%, ALMS vs. our LN cohort, respectively) who generally tend to present with more severe LN. Both gender and ethnicity are factors affecting the incidence and severity of LN, as well as treatment outcomes. There is evidence that Hispanic and African-American individuals have a higher incidence and prevalence rates of LN and they may also show different response to treatment.[43,44] Clinical studies should account for these ethnic disparities, as indicated by the National Institutes of Health Revitalization Act of 1993.[45] Some issues could certainly be improved if demographic profiles would be incorporated in trial designs, and medical systems were able to address poverty, lack of education, impaired access to trials, and language barrier. Ultimately, more diverse recruitment strategies should be used when enrolling minority groups to achieve a more representative patient population, which would lead to a better generalizability of the results.

The lack of transparency due to poor reporting rate can eventually cause serious damage; by preventing readers from evaluation of the validity and reliability of these trials, which may result in biased estimates of treatment effects. The CONSORT 2010 statement (Consolidated Standards of Reporting Trials) gives a clear guidance on the reporting of RCTs using an essential checklist.[46] The checklist includes the reporting of exclusion rates. Since this CONSORT was published, sadly, only 1 journal article included in this analysis followed these recommendations. We recommend that editors improve the reporting quality of clinical trials for transparency by giving authors clear guidance on items to be reported.

In summary, the present study was the first to evaluate how representative participants in published LN RCTs were in comparison with patients seen in usual clinical practice from a large tertiary lupus center. A third of newly diagnosed real-world patients with LN would have been excluded from LN RCTs due to strict eligibility criteria solely related to the severity of their renal disease. Although some trials have excellent validity, many do not; and factors determining their validity are rarely reported, preventing the clinician from using thoughtful judgment. Specifically, we highlight the need for more pragmatic trials designed for those with more severe LN.

DISCLOSURE

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