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NEPHROLOGY - REVIEW

Efficacy and safety of leflunomide in IgA nephropathy: a systematic review and meta-analysis

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Abstract

Background The optimal therapy for immunoglobulin A nephropathy (IgAN) remains uncertain. Leflunomide (LEF) is an immunosuppressive drug which may reduce deposition of glomerular autoantibodies and immune complexes. Several clinical trials were designed to evaluate the efficacy of LEF, but their results were controversial.

Methods Ovid Medline, Embase, the Cochrane Library, PubMed, and CNKI were systematically searched. Search terms included ("glomerulonephritis" OR "nephritis") AND ("immunoglobulin A" OR "IgA") AND "leflunomide". Studies in which patients were diagnosed with IgAN based on renal biopsy were included. Studies needed to report clinical outcomes via either short- or long-term clinical examination, remission rate, or complication rate.

Results Forty-four studies encompassing 1802 patients were included, of which 35 were randomized controlled trials. Results of 24 h post-treatment urine protein tests and serum creatinine tests were significantly lower in patients treat with LEF and corticosteroids (CS) or valsartan (ACEI) (CS + LEF or CS + ACEI) compared with patients treated with CS or ACEI alone ($P < 0.05$). More patients treated with CS + LEF (31.2%) achieved complete remission (CR) than patients treated with CS alone (22.2%) (RR = 0.71, 95% CI 0.59–0.85, $P < 0.05$). Although there was no significant difference in CR between patients treated with cyclophosphamide and CS (CS + CTX) and those treated with CS + LEF, the complication rate in the former group was higher (28.4%) than in the latter one (11.4%) (RR = 2.46, 95% CI 1.47–4.13, $P < 0.005$).

Conclusion LEF appears to improve renal function while decreasing loss of urine protein. Combination regimens including LEF were better and safer compared with CS or ACEI alone or combinations including CTX.

Keywords Leflunomide · IgA nephropathy · Treatment · Immunosuppressive agents

Introduction

Immunoglobulin A nephropathy (IgAN) is a primary glomerular disorder characterized by deposition of immunoglobulins (mainly IgA, and currently considered to be mainly IgA1) in the mesangial area [1]. First reported by Berger and Hinglais in 1968, IgAN is more prevalent in Asian countries compared with Western ones [2–5]. The clinical features of IgAN patients vary, but symptoms can manifest as proteinuria, elevated serum creatinine, signs of occult nephritis, nephrotic syndrome, and acute renal failure [6]. IgAN is the most common primary glomerulopathy worldwide [3, 5, 7]. Although IgAN was considered benign for many years, many patients eventually develop renal failure requiring renal replacement therapy or kidney transplantation. IgAN is, therefore, the leading cause of end-stage renal failure in China [5].

The pathogenesis of IgAN is not fully understood, but may involve infectious and environmental factors, heredity, and mucosal immunity [7, 8]. Since the proximate cause of disease is unknown and disease pathogenesis is multifactorial, there exists no specific curative therapy for IgAN. While IgAN cannot be cured, treatment can prevent progression of the disease [9]. Therefore, it important to identify which treatments are best able to protect kidney function and delay disease progression.

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Several studies have shown that immunosuppressive agents can be used to treat IgAN [10, 11]. Leflunomide (LEF) is an immunosuppressive drug which can reduce the proliferation of T cells and B cells by inhibition of dihydroorotate dehydrogenase activity [12, 13]. In recent years, clinical studies have found that LEF can be used to treat immune-mediated kidney diseases such as systemic lupus erythematosus, IgAN, and refractory nephrotic syndrome [14–16]. In glomerular diseases, LEF treatment can reduce the deposition of glomerular autoantibodies and immune complexes, thereby reducing kidney damage and reducing the risk of further deterioration of IgAN patients [16, 17].

Several institutions have carried out clinical trials of LEF therapy for IgAN [18–20]. However, the majority of these studies had a limited sample size and different control groups. For these reasons, the results of these studies were contradictory and have remained controversial. Therefore, we conducted a systematic review and meta-analysis of LEF therapy in IgAN patients, which we hope will be helpful for clinical decision making.

Materials and methods

This systematic literature search was reported in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [21].

Search strategy and study selection

The systematic review and meta-analysis were designed to assess the efficacy of LEF in treating IgAN. We systematically searched Ovid Medline, Embase, the Cochrane Library, and PubMed. In addition, since most of the clinical trials were undertaken in China, we also searched the Chinese CNKI and VIP databases. All databases were searched from inception to January 23, 2019. Search terms included ("glomerulonephritis" OR "nephritis") AND ("immunoglobulin A" OR "IgA") AND "leflunomide". The search strategy is shown in Supplemental Table 1. The grey literature was also reviewed in Google Scholar to identify additional relevant studies. After the search, all papers were imported into Endnote (Clarivate Analytic, version X6) to identify duplicate studies and to screen abstracts and titles.

Inclusion and exclusion criteria

All studies comparing the efficacy of LEF and a control drug in treating IgAN were included in our meta-analysis. All studies of patients aged 18 years or older who were diagnosed with IgAN based on kidney biopsy were included. Studies needed to report clinical outcomes via either short- or long-term clinical examination, remission rate, or complication rate. The exclusion criteria were: (i) pediatric IgAN; (ii) secondary IgAN or another nephritis; (iii) total sample size less than 20; (iv) animal experiment; (v) clinical data could not be extracted or lack of clinical outcome; and (iv) absence of a control group or comparison with another treatment such as traditional Chinese medicine. Conference proceedings were excluded unless the data could be fully extracted.

Literature screening and data extraction

Two reviewers (JW Yi and ZH He) independently screened the titles and abstracts based on inclusion and exclusion criteria. The full text was further analyzed if the inclusion and exclusion criteria could not be assessed based on the abstracts. Any disagreements in study selection were discussed with a third reviewer (SZ Xu).

Data were extracted including study characteristics (first author's name, publication year and title, recruitment year, country, institution, and study design), diagnosis (including IgAN grading), follow-up period, pre-treatment and post-treatment lab tests, remission rate, and complication rate. Lab tests included 24-h urine protein tests (UTP) and serum creatinine tests (SCR). The follow-up period needed to be at least 6 months, and lab test results were recorded at least 6 month post-treatment.

Quality assessment

Two investigators (JW Yi and S Feng) independently assessed the quality of the included studies. For randomized controlled trials (RCTs), the Cochrane Collaboration's tool for assessing risk of bias in RCTs was used to rate studies [22]. For observational cohort studies or case–control studies, the Newcastle–Ottawa Scale was used to assess study quality [23].

Definition and treatment guidelines

Patients treated with LEF received 40 mg of LEF per day for 3 days, after which the dose was reduced to 20 mg per day for at least 6 months. Corticosteroids (CS) were administered alone, usually in comparison with a combination therapy regimen (CS + LEF). In patients treated with CS, oral prednisone was administered at 1.0 mg/kg/day for 8–12 weeks with a maximum daily dose of 60 mg. Patients treated with cyclophosphamide (CTX) usually started at 8–12 mg/kg for 2 days every 2 weeks; the cumulative dose was 50–120 mg/kg and therapy was usually combined with CS and compared with CS + LEF. For patients diagnosed with secondary hypertension, valsartan was administered with a daily dose of 80 mg (ACEI) [17].

Table 1 Characteristics of included study

Author	Publish year	Recruitment year	Design	Sample (control vs. LEF)	Control group	Experimental group
Bian, Fuqiang	2019	2016.1–2017.1	RCT	45/45	CS	CS + LEF
Cao, Liou	2009	2003.6–2006.6	RCT	18/18	CS	CS + LEF
Chang, Jing	2011	2002.1–2009.1	RCT	24/28	CS + CTX	CS + LEF
Chen, Liping	2016	2014.5–2015.5	Retrospective cohort	43/42	CS	CS + LEF
Cheng, Genyang	2015	NA	RCT	42/42	ACEI	ACEI + LEF
Cui, Yingting	2018	2015.1–2017.12	RCT	75/75	CS	CS + LEF
Dong, Ji	2017	2013.1–2015.6	RCT	20/20	CS	CS + LEF
Feng, Huiliang	2012	2009.3–2011.3	RCT	22/22	CS	CS + LEF
Feng, Ling	2018	2015.4–2017.7	RCT	36/36	CS	CS + LEF
He, Xinsheng	2013	2012.3–2012.11	Retrospective cohort	24/28	CS	CS + LEF
Hu, Chunxian	2015	2010.10–2012.10	RCT	60/60	CS + CTX	CS + LEF
Hu, Yao	2018	2014.6–2016.6	RCT	40/40	CS	CS + LEF
Li, Tao	2011	NA	RCT	30/30	CS	CS + LEF
Lin, Yan	2009	2006.3–2007.12	RCT	20/20	ACEI	CS + LEF
Liu, Dian	2017	2015.4–2017.2	RCT	37/37	CS	CS + LEF
Lou, T	2006	2001.11–2003.11	RCT	22/24	ACEI	LEF
Luo, Nan	2015	2007.10–2014.10	Retrospective case–control	18/24	CS + CTX	CS + LEF
Mao, Feifei	2018	2014.8–2016.8	RCT	25/25	CS + ACEI	CS + ACEI + LEF
Min, L	2017	2004.6–2010.6	RCT	45/40	CS	CS + LEF
Shen, Jiansong	2010	2006.1–2007.12	RCT	20/20	CS + ACEI	CS + LEF + ACEI
Shen, Ping	2012	2008.5–2012.3	RCT	21/21	CS	CS + LEF
Shen, Shizhong	2016	2002.2–2015.1	RCT	32/28	CS	CS + LEF
Shi, Cailin	2017	2015.3–2017.1	RCT	54/54	CS	CS + LEF
Shi, Xiaojun	2017	2013.3–2015.11	RCT	20/20	CS	CS + LEF
Su, Xing	2013	2007.3–2011.3	Retrospective case–control	45/45	CS + CTX	CS + LEF
Sui, Jianying	2011	2008.10–2010.10	RCT	40/40	ACEI	*Tripterygium wilfordii* + LEF
Sun, Zhuxing	2009	2006.1–2008.12	RCT	35/35	CS + CTX	CS + LEF
Tao, Jun	2016	2013.1–2015.1	Retrospective cohort	40/40	CS	CS + LEF
Wang, Xiaofei	2016	2013–2–2015.4	RCT	40/40	CS + CTX	CS + LEF
Wu, Shengqing	2014	2008.1–2012.2	RCT	30/30	CS	CS + LEF
Xiang, Hongxiu	2017	2014.6–2016.1	RCT	49/49	CS	CS + LEF
Xu, Changan	2018	2015.2–2018.2	RCT	10/10	CS	CS + LEF
Yang, Dongsen	2010	2008.2–2010.2	RCT	20/20	CS	CS + LEF
Yang, Youqin	2016	2012.5–2014.5	RCT	52/52	ACEI	CS + LEF
Zeng, Lei	2015	2011.8–2014.9	RCT	32/32	CS	CS + LEF
Zhang, Chi	2014	2012.3–2014.3	Retrospective cohort	20/20	CS	CS + LEF
Zhang, Haifeng	2013	2010.1–2012.10	RCT	20/20	CS + CTX	CS + LEF
Zhang, Jianrong	2012	2005.5–2011.5	RCT	20/20	Cozaar	Cozaar + LEF
Zhang, Lewen	2010	2008.1–2010.1	Retrospective cohort	15/15	CS	CS + LEF
Zhao, Jingan	2018	2013.10–2016.5	RCT	48/48	CS	CS + LEF
Zhao, Qingrui	2015	2005.2–2014.6	RCT	45/45	CS	CS + LEF
Zhao, Xiaohua	2017	2015.1–2016.8	Retrospective cohort	33/32	CS	CS + LEF
Zhong, Zhuhan	2011	2007.9–2010.4	RCT	28/28	CS + CTX	CS + LEF
Zou, Yurong	2013	2009.6–2012.7	Retrospective cohort	25/32	CS + CTX	CS + LEF

NA not available, *RCT* randomized controlled trials, *CS* corticosteroid, *CTX* cyclophosphamide, *LEF* leflunomide, *ACEI* angiotensin-converting-enzyme inhibitor

Clinical evaluation was based on standard remission guidelines [16]. Complete remission (CR) was defined as UTP less than 0.3 g, albumin increasing to normal levels (> 35 g/L), and renal function remaining normal. Partial remission (PR) was defined as a decrease in UTP of > 50% with renal function improvement. Efficacy (E) was defined as a decrease in UTP > 25% but < 50% with renal function improvement. Deterioration was defined as a decline in renal function of > 30% with an increase in UTP of > 30% [16]. To balance baseline parameters and decrease bias related to pre-treatment lab tests, post-treatment lab tests were compared using subgroup analyses.

Statistical analysis

Review manager 5.3 (RevMan, freeware available from the Cochrane Collaboration) was used for statistical analysis. The risk ratio (RR) was used to compare dichotomous variables, and the standard mean difference (SMD) was used to compare post-treatment UTP and SCR. 95% confidence intervals (CIs) were reported, and statistical significance was assumed for values of $P < 0.05$. The I^2 statistic and the χ^2 test were used to evaluate heterogeneity ($P < 0.05$ with $I^2 \geq 50\%$ indicated the presence of heterogeneity). When heterogeneity was absent, a fixed-effects model was applied. By contrast, a random-effects model was applied in the presence of heterogeneity. Forest plots and funnel plots were used to assess publication bias.

Results

Study selection

After searching databases, 435 studies were identified, and 21 additional studies were identified from the grey literature. After screening titles and abstracts, 44 studies were included [16–20, 24–62]. A flow chart for study selection is shown in Fig. 1.

Characteristics of included studies

Among the 44 studies, 35 were RCTs [16–20, 26, 27, 29, 30, 32, 36, 38–42, 44–62]. Table 1 shows characteristics of the included studies. Publication dates ranged from 2006 to 2019 with recruitment periods between 2001 and 2017. Twenty-seven studies compared the efficacy of CS and CS + LEF, representing a total of 1802 patients (905 CS-treated patients and 897 CS + LEF-treated patients). Six studies compared the efficacy of ACEI and ACEI + LEF, representing a total of 364 patients (181 ACEI-treated patients and 183 ACEI + LEF-treated patients). Nine studies compared the efficacy of CTX and LEF (usually both combined with CS), representing a total of 607 patients (295 CS + CTX-treated patients and 312 CS + LEF-treated patients). The remaining two studies compared LEF with Cozaar and *Tripterygium wilfordii*, which did not permit comparison with a control. Male patients made up 53.99%

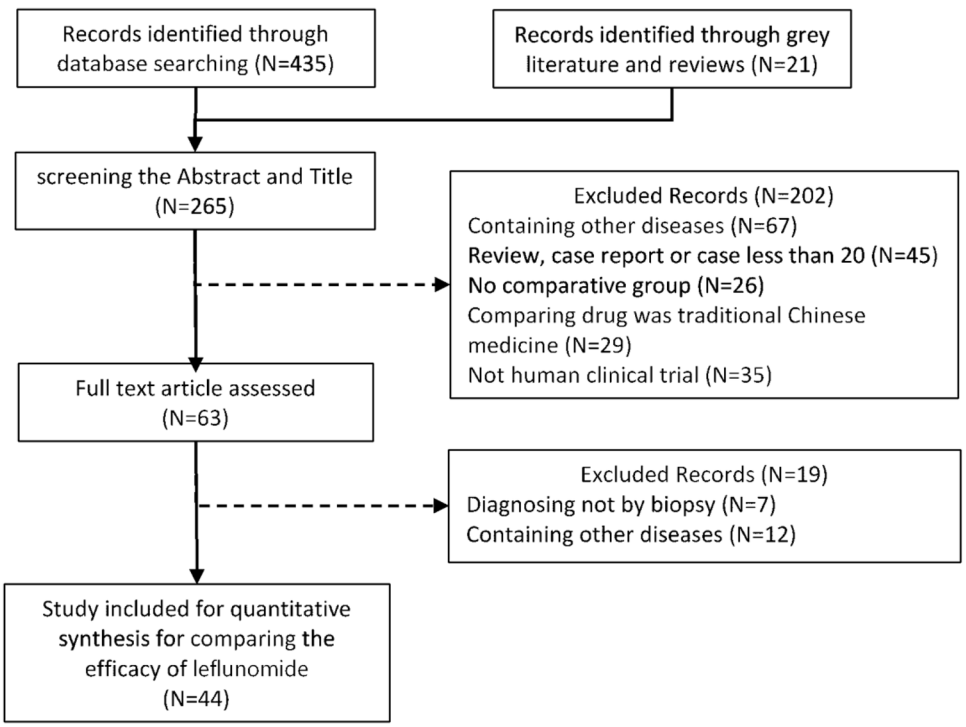

Fig. 1 Flow chart of the literature selection

(520/963) of the non-LEF group and 53.92% (495/918) of the LEF group. The median patient age was 36 years [interquartile range (IQR): 34–44 years] in the non-LEF group versus 36 years (IQR: 33–43 years) in the LEF group.

Quality assessment

The risk of bias graph for the included RCTs is shown in Fig. 2. In this analysis, seven items were assessed. According to the individual items, "low risk of bias", "high risk of bias", and "unknown risk of bias" categories were assigned to all included studies. The risk of bias in most included studies was unknown, as it was unclear if they used blinding methods (low bias risk in performance bias was assessed in 25.7% of studies, while low detection bias was assessed in 14.2% of studies). The individual risk of bias table is shown in Supplemental Figure 1.

Comparison of lab results after treatment

Comparisons of post-treatment UTP and SCR results are shown in Figs. 3 and 4. In terms of UTP, 25 studies

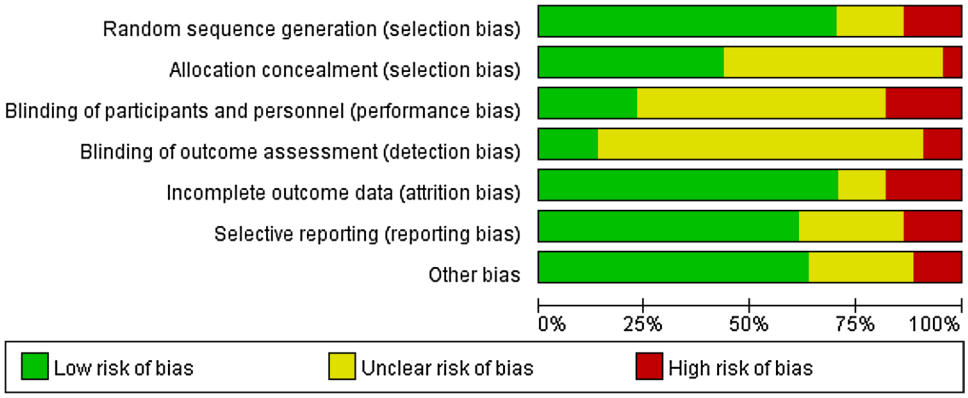

Fig. 2 Quality assessment of the risk of bias in all RCTs

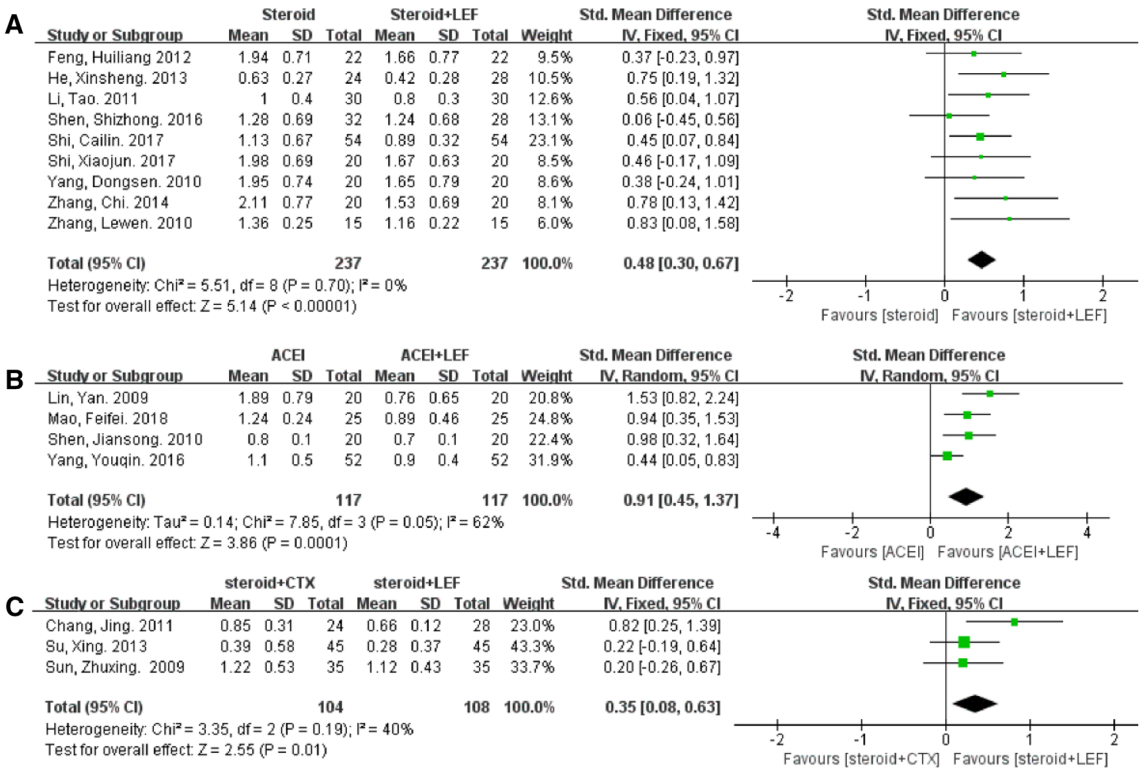

Fig. 3 Comparison of UTP after 6 months treatment for studies with pre-treatment median UTP less than 3 g (**a** CS vs. CS + LEF; **b** ACEI vs. ACEI + LEF; **c** CS + LEF vs. CS + CTX)

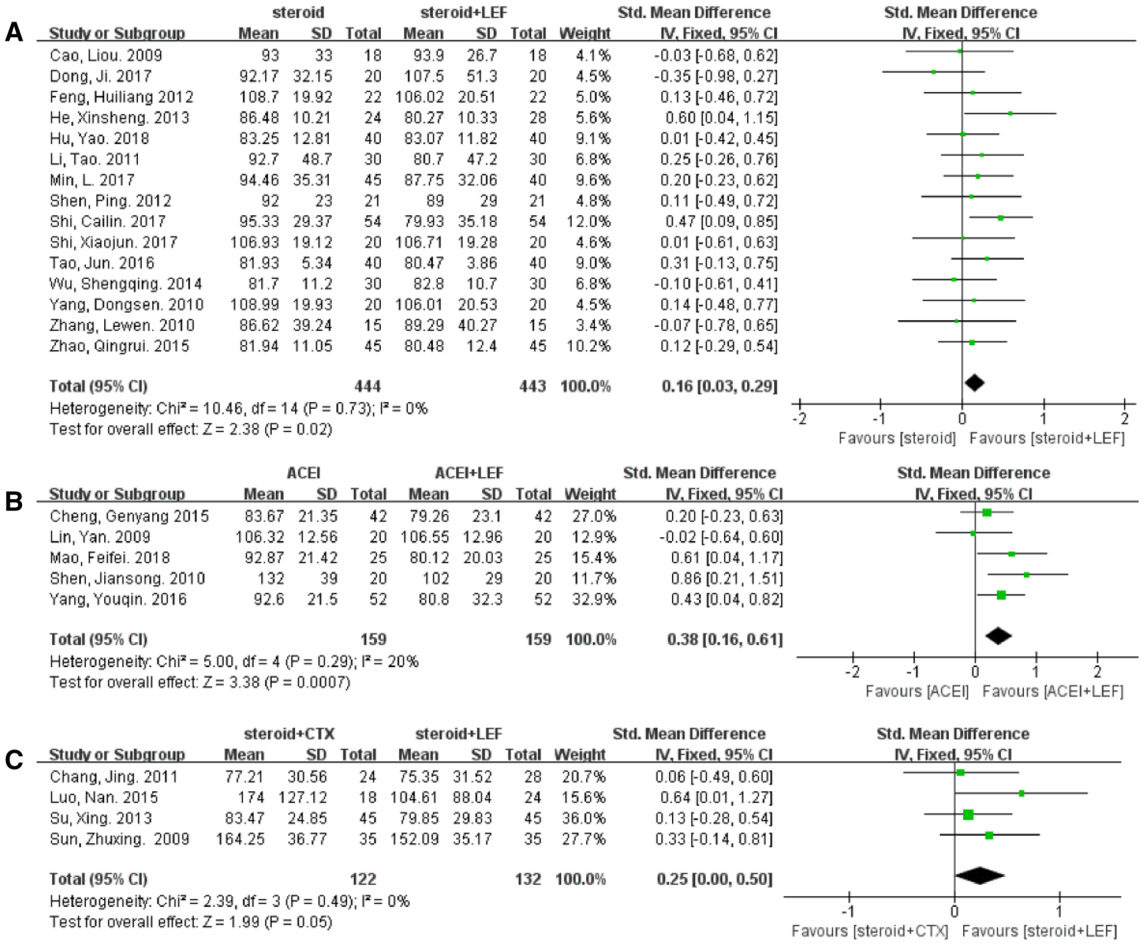

Fig. 4 Comparison of SCR after 6 months (**a** CS vs. CS + LEF; **b** ACEI vs. ACEI + LEF; **c** CS + LEF vs. CS + CTX)

contributed to the analysis (Supplemental Figure 2). Patients treated with LEF + CS had lower UTP scores 6 month post-treatment compared with patients treated with CS alone (SMD = 0.89, 95% CI 0.49–1.29, $P < 0.001$, $I^2 = 89\%$, random-effects model). Similarly, patients treated with LEF + ACEI achieved lower UTP scores than patients treated with ACEI alone (SMD = 0.91, 95% CI 0.45–1.37, $P < 0.001$, $I^2 = 62\%$, random-effects model). However, there was no significant post-treatment difference between the UTP scores of patients treated with CS + CTX and CS + LEF (SMD = 0.22, 95% CI − 0.21–0.65, $P = 0.32$, $I^2 = 65\%$, random-effects model).

Due to heterogeneity in pre-treatment UTP, studies with pre-treatment median UTP < 3.0 g were analyzed separately (Fig. 3). Patients treated with LEF + CS or LEF + ACEI had lower post-treatment UTP than patients treated with CS or ACEI alone (SMD = 0.48 and 0.91, respectively; $P < 0.001$; $I^2 = 0\%$ and 62%, respectively). Moreover, patients treated with LEF + CS had lower post-treatment UTP than those treated with CTX + CS (SMD = 0.35, 95%CI 0.08–0.63, $P = 0.01$, $I^2 = 40\%$).

For assessment of post-treatment SCR, 24 studies contributed to the analysis (Fig. 4). Patients treated with CS + LEF had lower SCR than those treated with CS alone (SMD = 0.16, 95% CI 0.03–0.29, $P = 0.02$, $I^2 = 0\%$, fixed-effects model, Fig. 4a). A significant difference was observed between patients treated with ACEI and those treated with ACEI + LEF (SMD = 0.38, 95% CI 0.16–0.61, $P < 0.005$, $I^2 = 20\%$, fixed-effects model, Fig. 4b). However, there was no significant difference between patients treated with CS + LEF and CS + CTX (SMD = 0.25, 95% CI 0.00–0.50, $P = 0.05$, $I^2 = 0\%$, fixed-effects model, Fig. 4c).

Remission rates

A comparison of CRs is shown in Fig. 5, for which 26 studies contributed to the analysis. A higher proportion of patients treated with CS + LEF achieved CRs (31.2%) than of patients treated with CS alone (22.2%) (RR = 0.71, 95% CI 0.59–0.85, $P < 0.05$, $I^2 = 28\%$, fixed-effects model, Fig. 5a). Patients treated with ACEI + LEF group also achieved CR more often than those treated

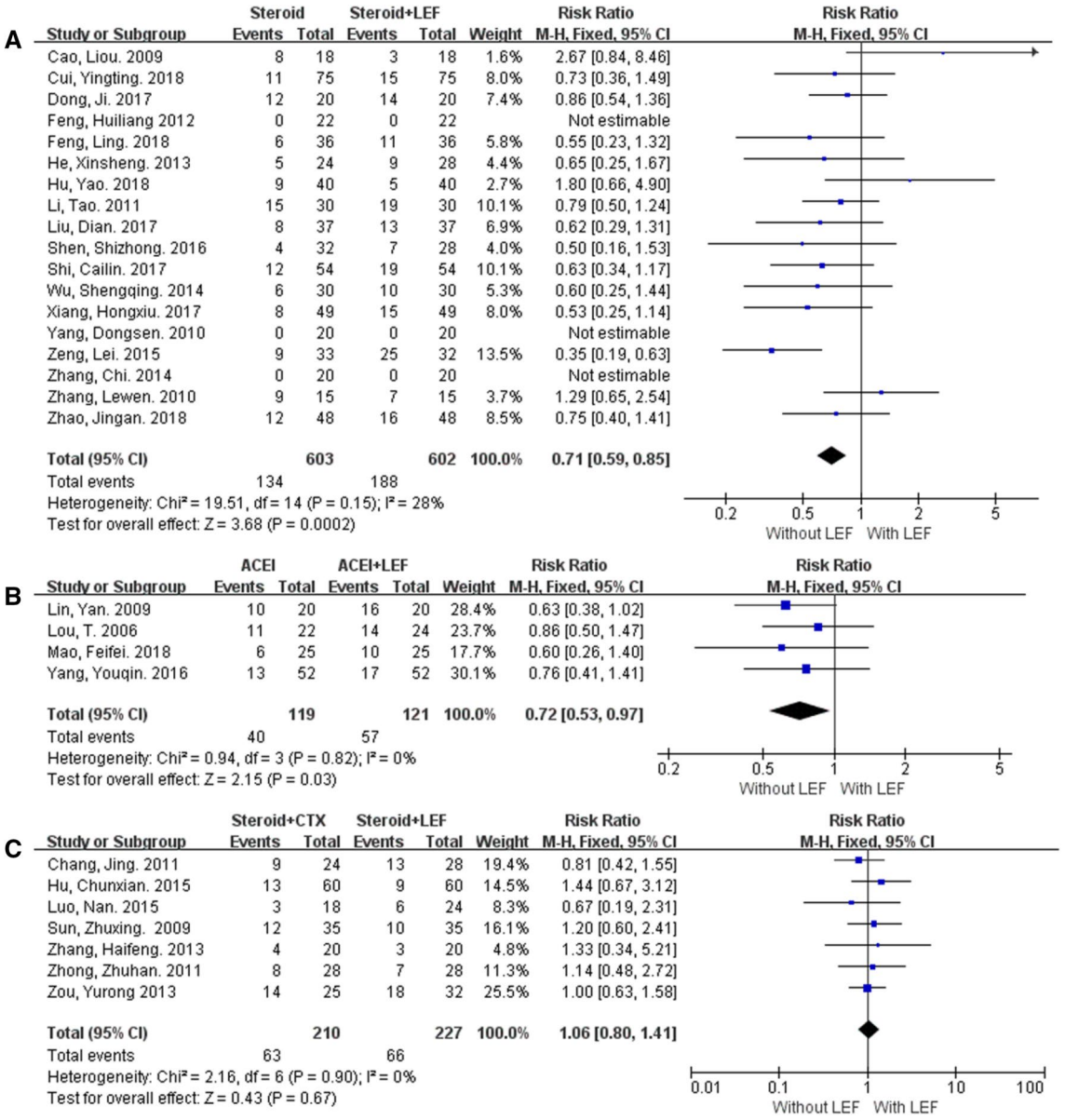

Fig. 5 Forest plot of the comparison of the complete release (**a** CS vs. CS + LEF; **b** ACEI vs. ACEI + LEF; **c** CS + LEF vs. CS + CTX)

with ACEI alone (47.1% versus 33.6%, RR = 0.72, 95% CI 0.53–0.97, $P = 0.03$, $I^2 = 0\%$, fixed-effects model, Fig. 5b). No significant differences were observed between patients treated with CS + CTX and CS + LEF (30% versus 29.1%, RR = 1.06, 95% CI 0.80–1.41, $P = 0.67$, $I^2 = 0\%$, fixed-effects model, Fig. 5c).

A total efficacy proportion was also calculated (the sum of CR + PR + E), as shown in Supplemental Figure 3. The results were similar to those for CR, in that patients treated with LEF + CS or LEF + ACEI had a higher total efficacy proportion than those treated with CS or ACEI alone. However, there was no significant difference in this proportion between patients treated with CS + CTX and those treated with CS + LEF ($P = 0.70$).

Complication rates

The forest plot comparing complication rates is shown in Fig. 6. Twenty-three studies contributed to this analysis. A minor statistical difference was observed between CS-treated and CS + LEF-treated patients (22.7% versus 17.4%, RR = 1.30, 95% CI 1.04–1.63, $P = 0.02$, $I^2 = 5\%$, fixed-effects model, Fig. 6a). There was no significant difference in complication rates between patients treated with ACEI

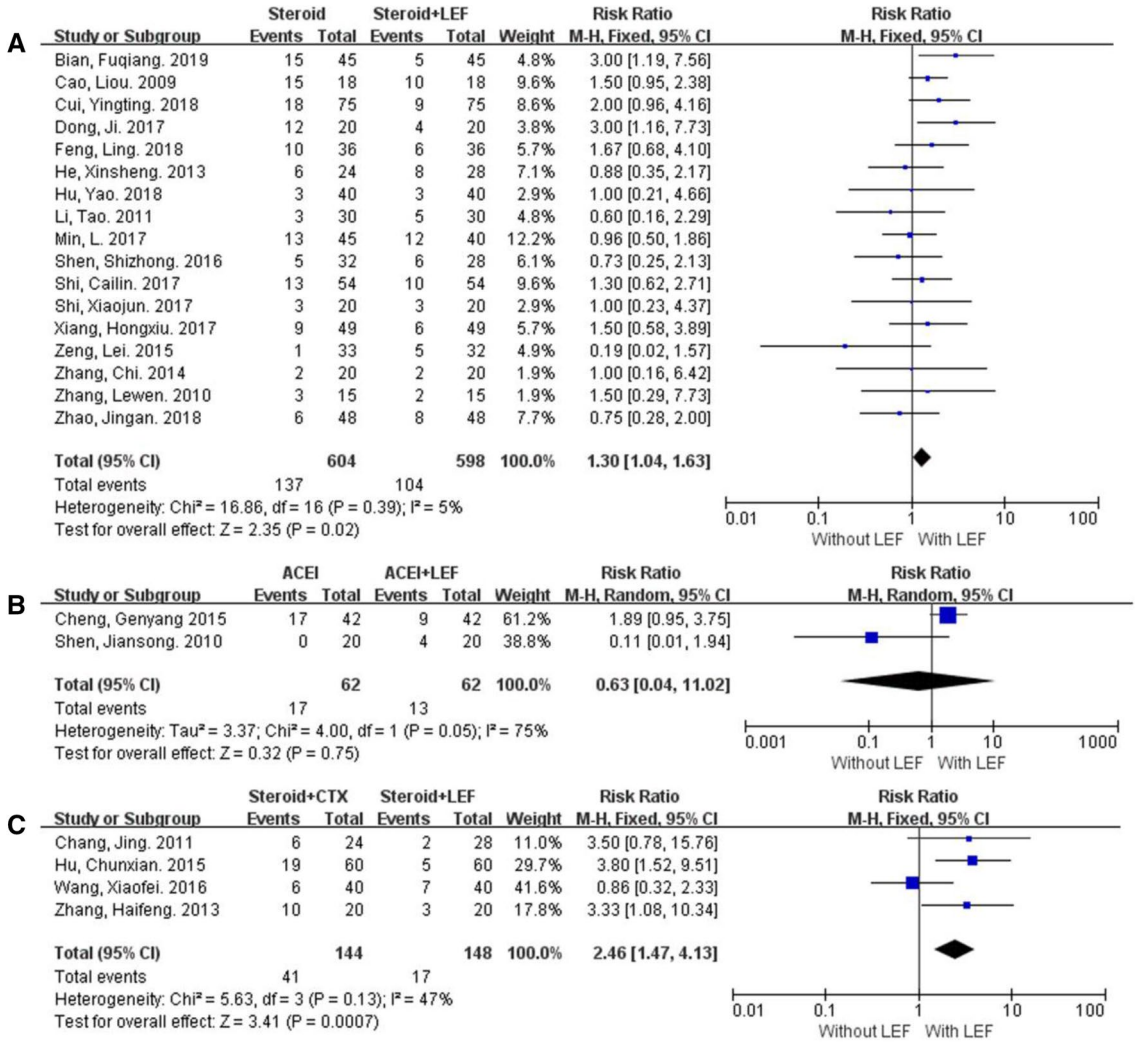

Fig. 6 Forest plot of the comparison of the complication rate (**a** CS vs. CS + LEF; **b** ACEI vs. ACEI + LEF; **c** CS + LEF vs. CS + CTX)

and ACEI + LEF (RR = 0.63, 95% CI 0.04–11.02, $P = 0.75$, $I^2 = 75\%$, random-effects model, Fig. 6b). The complication rate of patients treated with CS + CTX group was 28.4% compared with 11.4% in patients treated with CS + LEF (RR = 2.46, 95% CI 1.47–4.13, $P < 0.005$, $I^2 = 47\%$, fixed-effects model, Fig. 6c).

Discussion

Our systematic review and meta-analysis represents by far the most complete and most extensive conducted in the English language to date. The results of our study suggest that the combination of LEF with CS or ACEI can improve remission rates post-treatment, effectively reduce SCR and 24-h UTP, and also increase albumin levels. In comparisons of LEF and CTX, there was no difference in therapeutic effect, but adverse effects were significantly lower in LEF-treated patients. Overall, our results suggest that LEF is safe and effective in treating IgAN.

Because of the different clinical manifestations and pathological features of IgAN, there is a lack of uniformity in treatment guidelines for clinical practice [7]. Although ACEI and CS have been widely used to treat IgA nephropathy, satisfactory results are rarely achieved for patients with moderate to severe disease [63]. Increasing evidence supports a role for immunosuppressive agents in IgAN therapy [64, 65]. For example, mycophenolate mofetil (MMF) is rapidly hydrolyzed to yield the active metabolite mycophenolic acid upon oral administration, inhibiting non-competitive and reversible inhibition of hypoxanthine phosphate dehydrogenase and resulting in reduced guanine nucleotide synthesis. MMF inhibits DNA synthesis and selectively inhibits proliferation of T and B lymphocytes. MMF can also rapidly induce pathological changes in patients with persistent proteinuria [66]. Therefore, proteinuria is temporarily or

partially relieved and therapy has a long-term protective effect on renal function. However, the results of several meta-analyses of the short-term efficacy of MMF in reducing proteinuria and stabilizing serum creatinine were also controversial [67, 68]. Mizoribine (MZR), isolated from mold culture medium, is widely used in Japan for treating IgAN [68, 69]. Yoshikawa et al. used MZR, heparin–warfarin, dipyridamole, and hormone therapy to treat 23 IgAN patients with severe pathological changes. Over a 2-year follow-up period, 18 patients showed reduced proteinuria, but the proportion of patients with glomerular sclerosis did not change significantly. This result indicated that MZR can prevent progression of glomerular sclerosis and improve prognosis [69]. However, MZR induces mild gastrointestinal reactions and has myelosuppressive effects. Tacrolimus (FK506), a macrolide analog identified from mold fermentation, is a commonly used immunosuppressive drug. Kim et al. evaluated FK506 in the treatment of mild-to-moderate IgAN. Forty patients were randomly assigned to the FK506 or placebo group [70]. The blood concentration of FK506 was controlled at 5–10 ng/mL. The results showed that FK506 reduced proteinuria in patients with normal blood pressure, indicating that FK506 could replace ACEI in patients with IgAN who cannot tolerate antihypertensive drugs. Although fewer adverse reactions occurred to FK506, such as liver and kidney damage, hirsutism, and gingival hyperplasia, the side effects of elevated blood glucose are still clear and the drug should be used with caution [71].

LEF is a novel synthetic isoxazole anti-proliferative immunosuppressive agent that inhibits the activity of tyrosine kinases and NF-κB in T lymphocytes. Signal amplification and conduction inhibit immune responses. LEF also inhibits the activity of dihydrofolate dehydrogenase and cell-cycle-dependent kinases, further inhibiting the proliferation of T and B lymphocytes and immune responses [18, 72]. Some studies found that LEF affects the immune system by regulating the balance of T-cell subsets, mainly by downregulating the activity of CD4 + lymphocytes, reducing the differentiation of Th cells, and changing the Th1/Th2 ratio in the blood [17, 73]. Moreover, LEF can be rapidly converted into active metabolites in vivo, which can inhibit the production and action of inflammatory mediators and cytokines such as IL-1, TNF, and NF–κB in vivo. These cytokines, interleukins, and resulting IgA play an important role in the occurrence and development of nephropathy [16]. Other studies established a rat kidney disease model and compared the protective effects of hormones in nephropathy [74]. Hormones could significantly reduce deposition of immune complexes in the mesangial area of renal tissue, which might be related to downregulation of MCP-1 and TGF-β. In clinical use, LEF is as effective as methotrexate and sulfasalazine for the treatment of rheumatoid arthritis [15]. Bartlett et al. also found that LEF reduced glomerular disease itself. Moreover, the amount of antibody and immune complex deposited, as well as autoantibody production, were reduced [75]. In a mouse model of IgAN, both LEF and CS were found to reduce deposition of glomerular mesangial immune complex, although LEF was more effective [76].

It is well established that changes in albumin levels in humans are related to a variety of factors such as nutritional status, mental health, urinary protein excretion levels, drugs, diseases, and other factors. Many clinical studies and animal experiments have shown that urinary protein can induce renal tubular epithelial cell damage, and thus, urinary protein has been used as an independent factor in evaluating renal prognosis [77, 78]. Our study demonstrated that LEF + CS can reduce urinary protein levels and improve renal function in IgAN patients, which can significantly improve overall remission rates compared with CS alone. However, when comparing post-treatment UTP between groups, significant heterogeneity was apparent due to pre-treatment differences in baseline median UTP. Thus, we independently compared the impact of treatment in patients with pre-treatment median UTP < 3 g. LEF reduced urinary protein effectively even when bias was controlled. Moreover, LEF did not increase the incidence of adverse reactions in patients and could reduce the amount of CS administered to some extent, thereby reducing the risk of CS-induced adverse reactions such as infection, obesity, and osteoporosis [18]. We also found that LEF + ACEI reduced proteinuria more effectively than ACEI alone. Thus, LEF may be used when the effects of ACEI alone are not satisfactory. Similarly, there were no significant adverse effects observed in patients treated with ACEI + LEF compared with ACEI alone. We also compared LEF + CS and CTX + CS for treatment of IgAN. Although the effects of CTX and LEF were similar, the adverse effects of LEF were significantly lower than CTX. LEF has high specificity, few side effects, convenient oral administration, and strong patient compliance. In addition to the clinical application of CTX, LEF may represent a novel clinical option for IgAN, despite the fact that there no large studies including multiple centers have supported its clinical use.

Our study also had some limitations. First, we only compared LEF with CS, ACEI, and CTX, as few studies reported comparisons with other treatments. Second, the majority of studies were from Chinese institutions, and the patients involved were mainly from Asian populations. Large, multicenter, prospective studies involving global populations are still needed. Furthermore, for most of the RCTs included in our study, some degree of bias in random design, allocation concealment, and blinding was unavoidable. In addition, the follow-up time varied from study to study. To avoid bias caused by long-term follow-up, we only made comparisons at 6-month follow-up. For comparisons of long-term prognosis, more than 1 year post-treatment, additional studies will be needed.

Conclusion

In conclusion, LEF was a safe and effective treatment for IgAN and could improve renal function while decreasing loss of urine protein. Combinations of LEF + CS and LEF + ACEI were superior to CS or ACEI alone, and patients treated with these regimens did not have increased adverse effects. Patients tolerated LEF better than CTX.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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