Immunosuppressive agents versus steroids in the treatment of IgA nephropathy-induced proteinuria: A meta-analysis

YANLI LIU, JUN XIAO, XINTIAN SHI, GUOJUN HAO, QINKAI CHEN, JING ZHOU and XIN WEI

Department of Nephrology, The First Affiliated Hospital, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

Abstract. Immunoglobulin A nephropathy (IgAN) is one of the most common types of primary glomerular disease. Immunosuppressive treatment for patients with IgAN remains controversial. The present meta-analysis aimed to assess the efficacy and safety of various immunosuppressive agents compared with steroids in patients with IgAN and moderate to severe proteinuria. PubMed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Weipu, Chinese Biomedical Literature Database and Qinghuatongfang were searched for relevant randomized controlled trials (RCTs) published between 1990 and September 2013. All eligible studies (biopsy proven IgA nephropathy, use of immunosuppressive agents) measured urinary protein excretion and proteinuria remission. Data were analyzed with the random effects model using Review Manager. A total of 29 RCTs were included, involving 1,466 patients. Compared with steroids, immunosuppressive agents, including azathioprine (AZA) [complete response (CR)/partial response (PR); relative risk (RR), 3.43; 95% confidence interval (CI) 1.92-6.12; P<0.0001], mycophenolate mofetil (MMF) (CR/PR; RR, 2.19; 95% CI, 1.25-3.85; P=0.006) and leflunomide (LET) (CR/PR; RR, 2.64; 95% CI, 1.80-3.86; P<0.00001) resulted in increased partial or complete proteinuria remission. Cyclophosphamide (CTX) resulted in a higher reduction of urinary protein excretion than steroids (SMD, 0.91; 95% CI, 0.41-1.41; P=0.0004)). Compared to CTX, LET showed higher effectiveness (CR/PR; RR, 2.01; 95% CI, 1.08-3.75; P=0.03) with a lower incidence of adverse events. The present meta-analysis, which is based on IgAN patients, suggested that AZA, MMF, LET and CTX are effective in reducing proteinuria levels, with acceptable side effects. Therefore, immunosuppressive agents may be considered promising therapeutic agents for the treatment of IgAN and should be investigated further in large sample size, high-quality studies.

Introduction

Immunoglobulin A nephropathy (IgAN) is a type of immune complex-mediated glomerulonephritis that is pathologically characterized by the deposition of IgA immune complexes in the mesangium of the kidney (1). IgAN is the most common form of primary glomerulonephritis worldwide, particularly in China (2). In addition, 15-20% of patients with IgAN develop end-stage renal failure (ESRD) within 10 years, and 30-40% within 20 years (3-5). Proteinuria is regarded as the most severe risk factor for unfavorable renal prognosis, and its reduction is an important therapeutic goal in clinical practice (6).

Optimized supportive therapy is the key strategy for patients with IgAN who are at risk of progression, with renin-angiotensin-system (RAS) inhibitors being the most common treatment. However, the optimal immunosuppressive treatment strategy for patients with IgAN suffering from moderate to severe proteinuria remains uncertain. According to the guidelines outlined by the clinical practice guideline for glomerulonephritis (7), patients with IgAN who suffer from persistent proteinuria of >1 g/day following 6 months of treatment with RAS inhibitors are recommended to undergo corticosteroid therapy. There is an ongoing debate over the efficacy and safety of immunosuppressive agents other than glucocorticoid monotherapy in patients with IgAN who present with moderate to severe proteinuria; specifically, the use of relatively novel agents, including leflunomide (LET) and mycophenolate mofetil (MMF).

Increasing attention has been paid to the role of immunosuppressive agents in the treatment of patients with IgAN. The present report aimed to generate a meta-analysis from the most up-to-date studies regarding the safety and efficacy of various immunosuppressive therapeutic strategies for the treatment of patients with IgAN, in order to provide comprehensive current information to nephrologists to aid decision making. China has the largest population worldwide, and has a high incidence of IgAN. In order to exclude interferences that may be due to the ethnicity of patients, the present meta-analysis was performed using studies involving Chinese patients exclusively.

Correspondence to: Dr Xin Wei or Professor Jing Zhou, Department of Nephrology, The First Affiliated Hospital, Nanchang University, 17 Yong Wai Zheng Street, Nanchang, Jiangxi 330006, P.R. China
E-mail: weixin842270@126.com
E-mail: zhouj@medmail.com.cn

Methods

Information sources and search strategy. All randomized controlled trials (RCTs) that assessed the efficacy and safety of various immunosuppressive agents in the treatment of Chinese patients with IgAN between 1990 and September 2013 were included in the present meta-analysis. Numerous databases were searched for eligible RCTs, including: PubMed, Excerpta Medica database, the Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Weipu, Chinese Biomedical Literature Database and Qinghuatongfang. The following medical terms and phrases were used for the search: 'Immunoglobulin A nephropathy'; 'IgA nephropathy'; 'Berger disease'; 'glomerulonephritis'; 'RCT'; 'controlled clinical trial' and 'immunosuppressive therapy'. Only RCTs published in either English or Chinese were considered to be eligible. The title and abstract of the search results were analyzed by two independent investigators. According to the inclusion criteria, reference lists from all identified articles were also searched.

Inclusion criteria. The following inclusion criteria were used in the present meta-analysis: (i) Prospective RCTs comparing various immunosuppressive agents; (ii) the selected patients with IgAN were Chinese, whether adults or children; (iii) diagnosis of IgAN was performed via renal biopsy; and (iv) the study was published in English or Chinese.

Exclusion criteria. Studies were excluded if they: (i) Assessed secondary types of IgAN or patients who were not Chinese; (ii) were designed without randomization, such as retrospective studies and descriptive studies; (iii) included the use of traditional Chinese medicine, with its unknown additional effects on immunosuppressive agents and uncertain doses of active components; (iv) only assessed corticosteroids; or (v) failed to exclude patients with other systemic diseases, such as lupus, Henoch-Schonlein purpura and rheumatoid arthritis.

Study selection. All of the studies included in the present meta-analysis were independently assessed by two reviewers, in accordance with the set criteria, through retrieved abstracts and, if necessary the full texts. Disagreements were resolved in consultation with a third reviewer until a consensus was reached.

Data extraction. Data were independently extracted from each study by two reviewers using a predesigned review form (Microsoft Office Excel 2010; Microsoft Corporation, Redmond, WA, USA); disagreements were resolved in discussion with a third reviewer until a consensus was reached.

The review form included the following data: First author and unit of each study; year of publication; country of publication; journal; patient characteristics, including age, gender and ethnicity; interventions, including type of immunosuppressive agents, dose and usage; and the methodology of the RCTs. Baseline, final proteinuria, serum creatinine and serum albumin levels, and the type of outcome (complete remission, partial remission and total effective rate) were recorded. In addition, the presence of side effects, including: Elevated levels of liver enzymes; hypertension; diabetes; glaucoma; cataracts; leukocytopenia and infection, were recorded.

Assessments of methodological quality. The respective qualities of the RCTs were independently assessed by two authors, using the scoring system developed by Jadad *et al* (8). The quality scoring system was as follows: (i) Generation of random sequences (2=appropriate, computer generated random numbers or similar methods; 1=unknown, randomized trials but did not describe the method of random distribution; 0=inappropriate, adopted the method of alternate distribution such as single and double); (ii) randomization concealment (2=appropriate, clinicians and patients matched by unpredictable assigned sequence method; 1=unknown, only stating the use of a random number table or other random allocation scheme; 0=description not clear); (iii) blinding method (2=appropriate, using the identical placebo or similar methods; 1=not clear, statement for blinding method, but no description available; 0=inappropriate, did not adopt the method of double blinding, or inappropriate blinding such as tablets and injections); (iv) withdrawal (1=described the withdrawal or exit and indicated the reasons; 0=did not describe the withdrawal or exit or the reasons thereof).

Data analysis and statistical methods. Statistical analyses were performed using Review Manager software (version 5.0.2; The Cochrane Collaboration, Oxford, UK). Two-sided P-values were obtained via the χ^2 test and P<0.05 was considered to indicate a statistically significant difference. Dichotomous outcome data were analyzed using the odds ratio, 95% confidence intervals (CI), and the standardized mean difference (SMD). 95% CI was used as a summary estimator for continuous outcomes. The heterogeneity of the trial results was investigated visually by examination of the plots and statistically via the heterogeneity I^2 values. In order to reveal possible publication bias, funnel plots of study size vs. effect size were visually assessed for the total clinical remission rate.

Results

Study characteristics. The combined search identified 1,747 articles, of which 1,653 were excluded during the initial review. The main reasons for the exclusion of eligible RCTs were: Non-randomization, evaluation of other interventions (e.g. non-immunosuppressive agents), and a lack of renal outcomes of interest. Furthermore, animal and basic research studies were excluded, in addition to a number of review articles on the topic. The full-text versions of the remaining 94 articles were analyzed and a further 64 articles were excluded for similar reasons. Overall, 29 studies (9-37), including 1,466 patients, were included in the present meta-analysis (Fig. 1). The following comparisons were analyzed: MMF (or plus steroid) vs. steroid therapy alone (n=6); azathioprine (AZA) (or plus steroid) vs. steroid (n=5); LET (or plus steroid) vs. CTX (or plus steroid) (n=4); CTX (or plus steroid) vs. steroid (n=2). In 13 studies, LET was involved in the comparison. The characteristics of the included RCTs are shown in Table I.

Effects of interventions
AZA (or plus steroid) vs. steroid. Five RCTs (9-13) involving 292 patients compared the administration of AZA (or plus steroids) with steroid therapy. AZA (2-5 mg/kg/day) was admin-

Table I. Characteristics of the included trials.

Study (reference)	Number of patients	Mean age (years)	Length (months)	Baseline proteinuria (g/day)	Initial dose of immunosuppressive agents (per day)	Quality grade
AZA (or plus steroid) vs. steroid						
Huang S (9)	36	30.8/30.8	9	1.78±1.11/1.82±1.23	2 mg/kg AZA	3
Kuang B (10)	64	18.0-68.0[a]	6	0.39±0.09/0.38±0.09	2 mg/kg AZA	1
Li YN (11)	42	18.0-65.0[a]	12	1.41±1.29/1.32±0.91	1.5 mg/kg AZA	3
Ma FL (12)	80	37.1/37.5	NC	1.80±1.17/1.83±1.52	2 mg/kg AZA	2
Xu H (13)	70	38.4/35.2	18	38.42±12.80/35.26±13.27	2 mg/kg AZA	4
MMF (or plus steroid) vs. steroid						
Tang SC (18)	40	42.1/43.3	8	1.80±0.21/1.87±0.28	2 g (weight, ≥60kg) or 1.5 g (weight, <60kg) MMF	3
Chen XM (14)	62	28.0/29.0	24	3.20±1.70/2.90±1.50	1.0 g (weight. <50kg) or 1.5 g (weight, >50kg) MMF	2
Chen XSh (15)	39	42.7/38.6	12	NC	1.5 g MMF	3
Guo QY (16)	34	8.7/9.4	12	0.97±0.34/1.13±0.23	800-1000 mg/m² MMF	2
Huang Z (17)	38	34.0/32.0	2	6.71±5.53/5.89±4.90	0.5-2 gMMF	2
Wang WM (19)	40	40.0/39.4	12	1.75±1.60/1.51±0.92	1.0-1.5 g MMF (weight, <50kg is 1.0g)	3
LET (or plus steroid) vs. steroid						
Lou TQ (25)	55	33.0/33.0	6	1.30±0.70/1.60±0.80	60 mg LET	4
Yang FY (30)	82	36.6/38.2	6	2.60±1.40/2.50±1.20	50 mg LET	4
Hu RH (22)	45	42.7/42.7	9	2.16±0.64/2.08±0.73	50 mg LET	3
Zhang Y (32)	42	16-68[a]	6	2.85±0.80/NC	50 mg LET	3
Wang L (29)	36	36.3/34.2	6	2.38±1.31/2.42±1.28	50 mg LET	2
Fu Q (21)	37	32.6/36.5	1	2.56±0.90 /2.48±0.82	50 mg LET	3
Li T (24)	60	36.4/37.7	6	2.40±1.30/2.50±1.40	50 mg LET	2
Cao LO (20)	36	40.0/38.0	6	2.4(1.4-4.0)/2.6(1.7-3.1)	40 mg LET	3
Huang YX (23)	62	43.5/43.5	6	2.30±1.30/2.20±1.20	40 mg LET	4
Pu L (26)	60	36.2/37.4	6	2.10±0.94/2.08±1.03	20 mg LET	3
Zhang LW (31)	30	43.5 /42.8	6	2.43±1.32/2.24±1.14	50 mg LET	3
Sun MD (28)	36	37.0/37.0	3	2.68 ±0.68/2.66±0.69	50 mg LET	3
Shen P (27)	42	32.5/31.4	6	3.16±1.42/3.08±1.52	50 mg LET	3
CTX (or plus steroid) vs. steroid						
Wang WM (19)	40	39.5/39.4	12	1.74±1.06/1.51±0.92	0.5-0.75 g/m²CTX	3
Liu Y (33)	32	NC	12	1.55±0.44/1.38±0.62	8-12 mg/kg CTX	3
LET (or plus steroid) vs. CTX (or plus steroid)						
Guo M (34)	60	NC	28	5.12±1.08/5.14±1.34	50 mg LET; 8-12 mg/kg CTX	3
Zhong ShH (37)	56	NC	7	5.16±1.32/5.10±1.07	50 mg LET; 8-12 mg/kg CTX	3
Zhang HF (36)	40	43.7/43.7	4	NC	50 mg LET; 8-12 mg/kg CTX	4
Sun ZhX (35)	70	35.7/35.7	12	2.61±1.38/2.54±1.28	50 mg LET; 0.75 g/m²CTX	3

AZA, azathioprine; MMF, mycophenolatemofetil; LET, leflunomide; CTX, cyclophosphamide; NC, not clear. [a]Age range.
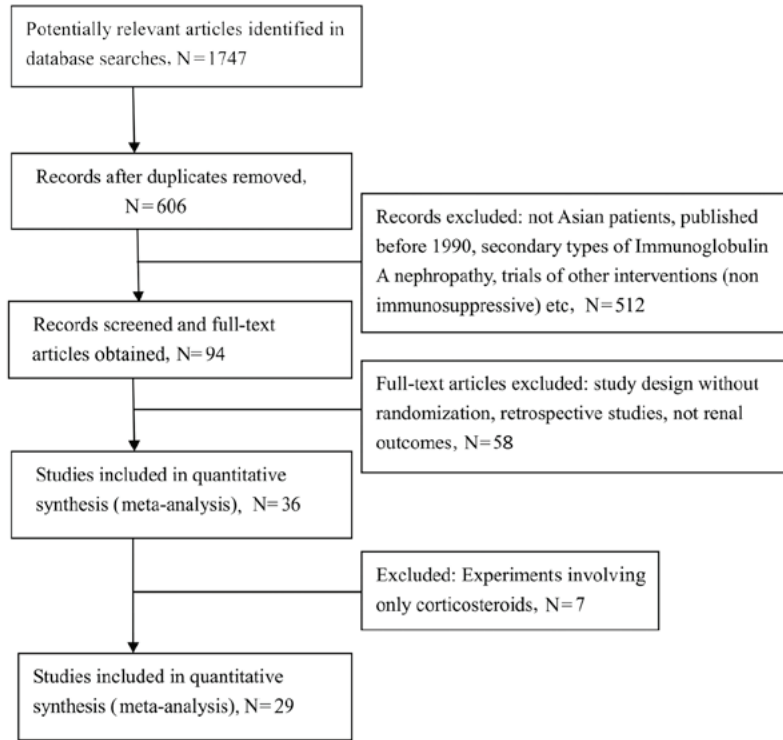
Figure 1. Flow diagram outlining the number of citations identified, retrieved and included in the final meta-analysis.
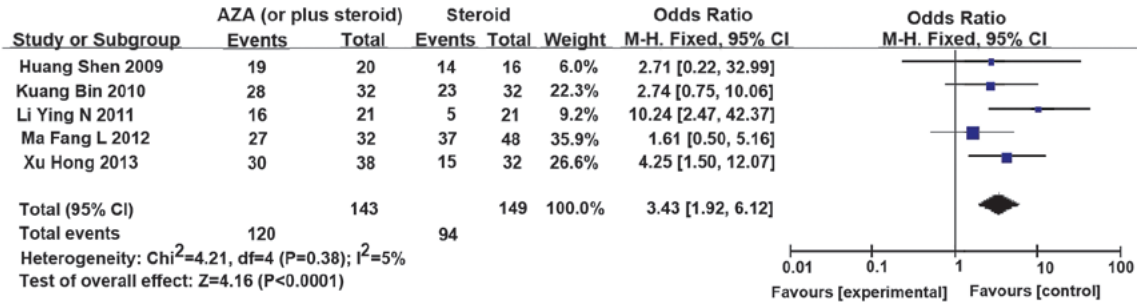

Figure 2. Complete/partial proteinuria remission rates in randomized controlled trials comparing AZA (or plus steroid) treatment with steroid treatment alone in patients with immunoglobulin A nephropathy. AZA, azathioprine; M-H, Mantel-Haenszel; CI, confidence interval.
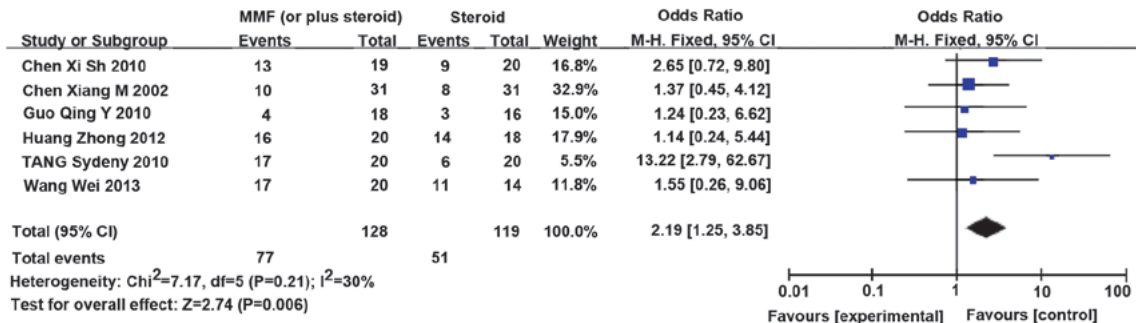

Figure 3. Complete/partial proteinuria remission rates in randomized controlled trials comparing MMF (or plus steroid) treatment with steroid treatment alone in patients with immunoglobulin A nephropathy. MMF, mycophenolatemofetil; M-H, Mantel-Haenszel; CI, confidence interval.

istered for 6-24 months. Prednisolone (0.8-1.0 mg/kg/day) was administered for 4-8 weeks and subsequently tapered off within one year (9-13). Patients receiving AZA demonstrated significantly increased complete response (CR)/partial response (CR) proteinuria remission rates [CR/PR; relative risk (RR), 3.43; 95% confidence interval (CI), 1.92-6.12, P<0.0001] (Fig. 2), as compared with the steroid therapy alone.
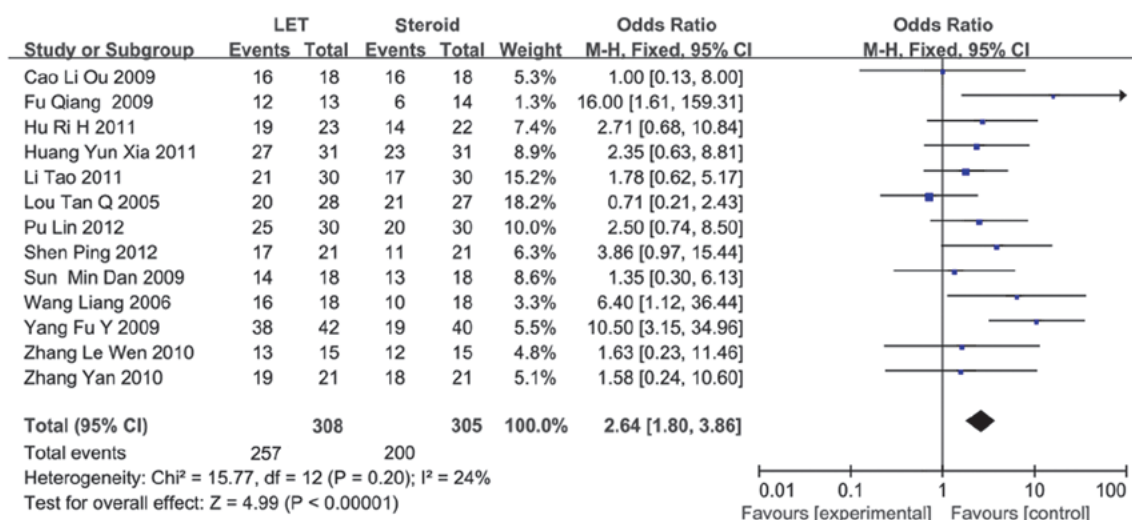
Figure 4. Complete/partial proteinuria remission rates in randomized controlled trials comparing LET (or plus steroid) treatment with steroid treatment alone. LET, leflunomide; M-H, Mantel-Haenszel; CI, confidence interval.
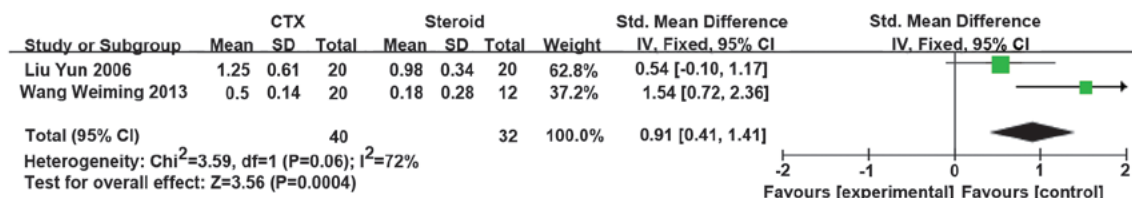

Figure 5. Reductions in the excretion of urinary protein in randomized controlled trials comparing CTX (or plus steroid) treatment and steroid treatment alone in patients with immunoglobulin A nephropathy. CTX, cyclophosphamide; SD, standard deviation; IV, inverse variance; CI, confidence interval.
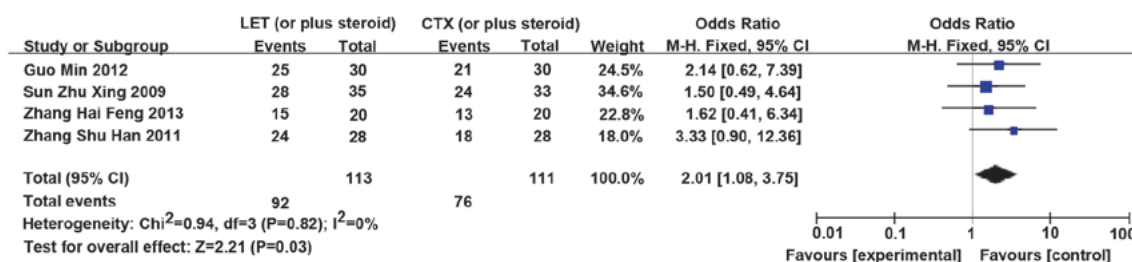

Figure 6. Complete/partial remission proteinuria rates in randomized controlled trials comparing LET (or plus steroid) and CTX (or plus steroid) treatment in patients with immunoglobulin A nephropathy. LET, leflunomide; CTX, cyclophosphamide; OR, odds ratio; CI, confidence interval.

MMF (or plus steroid) vs. steroid. Six RCTs (14-19) involving 253 patients compared MMF (or plus steroid) with steroid therapy alone. MMF (1.0-2.0 g/day) was orally administered for 3-6 months, and gradually tapered thereafter. The immunosuppressive treatment lasted for <12 months (14-19). Patients receiving MMF demonstrated significantly increased CR/PR proteinuria remission rates (CR/PR; RR, 2.19; 95% CI, 1.25-3.85, P=0.006) (Fig. 3), as compared with the steroid therapy alone.

LET (or plus steroid) vs. steroid. A total of 13 RCTs (20-32) involving 623 patients compared LET (or plus steroid) with steroid therapy alone. LET (50 mg/day) was orally administered for 3 days, reduced to 20-30 mg/day for 3 months, and subsequently tapered (20-32). LET demonstrated a marked advantage on CR/PR proteinuria remission, as compared with

the steroid therapy (CR/PR; RR, 2.64; 95% CI, 1.80-3.86; P<0.00001) (Fig. 4).

CTX (or plus steroid) vs. steroid. Two RCTs (19,33) involving 72 patients compared CTX (or plus steroid) treatment with steroid therapy alone. CTX (0.5-0.75 g/m^2) was intravenously administered in monthly pulses for six months, followed by quarterly pulses for the next six months. The immunosuppressive therapy lasted for 12 months in total (19-33). Patients receiving CTX (or plus steroid) demonstrated markedly increased reductions in urinary protein excretion levels by the end of treatment, as compared with patients treated with steroid therapy exclusively (SMD, 0.91; 95% CI, 0.41-1.41; P=0.0004) (Fig. 5).

LET (or plus steroid) vs. CTX (or plus steroid). Four RCTs (34-37) involving 226 patients compared LET (or plus
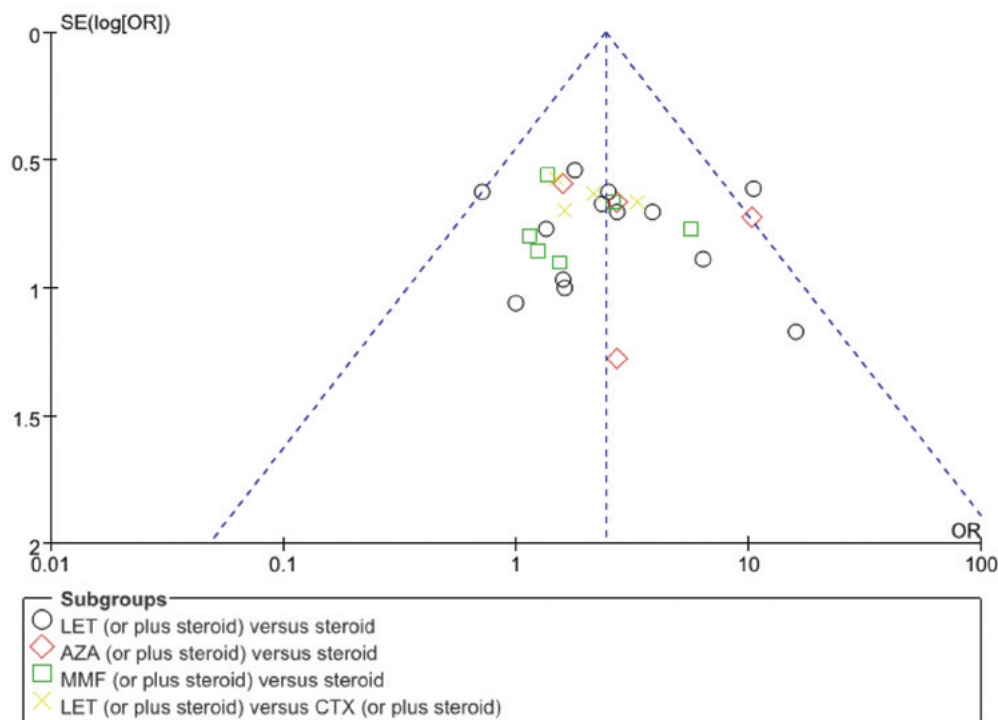
Figure 7. Funnel plot analysis of the complete and partial rates of proteinuria remission in the four comparison groups. AZA, azathioprine; MMF, mycophenolatemofetil; LET, leflunomide; CTX, cyclophosphamide; SE, standard error; OR, odds ratio.

steroid) with CTX (or plus steroid). LET (50 mg/day) was orally administered for 3 days, tapered, and subsequently reduced to 20 mg/day for 3 months (34-37). LET was significantly more effective in inducing remission, as compared with CTX (CR/PR; RR, 2.01; 95% CI, 1.08-3.75; P=0.03) (Fig. 6).

Side effects. Although it is challenging to statistically analyze the side effects in a single comparison, the major side effects for each agent were recorded. A total of 143 patients were treated with AZA, and adverse events were reported in 79 patients, including: Myelosuppression (n=5; 6.3%), liver dysfunction (n=6; 7.6%), and digestive symptoms (n=8; 0.12%). Infection was the most frequent side effect of AZA (14/79, 17.7%). A total of 16 patients (14.8%) treated with MMF demonstrated digestive symptoms; whereas a further 4 patients (3.7%) exhibited elevated liver enzymes. A total of 13/267 patients (4.7%) treated with LET demonstrated elevated liver enzymes, and a further 10 patients (3.7%) exhibited digestive symptoms.

No obvious nephrotoxicity directly related to the administration of immunosuppressive agents was demonstrated. In the 'LET (or plus steroid) vs. CTX (or plus steroid)' comparison, 9 and 13 patients treated with LET and CTX, respectively, demonstrated liver dysfunction; whereas 1 and 3 patients receiving CTX and LET, respectively, demonstrated digestive symptoms. Furthermore, leukocytopenia was detected in 6 patients treated with CTX, whereas 5 individuals treated with LET demonstrated alopecia.

Publication bias and sensitivity analysis. Publication bias was examined using funnel plots, which did not show any significant visual asymmetry (Fig. 7). Furthermore, in order to assess the robustness of the meta-analysis results, a sensitivity analysis focusing on the patients and the quality of the RCTs was conducted. Analysis was performed by excluding low quality RCTs. As outlined in Table I, the quality scores of all included RCTs were not high; therefore, any RCTs scoring less than 3 points were excluded (n=7). This sensitivity analysis did not substantially change the results of the comparisons.

Discussion

IgAN, which was initially identified by Berger and Hinglais in 1968 (1), is the most common form of primary glomerular nephritis in Asia. The immunological mechanisms associated with the development and progression of IgAN suggest that immunosuppressive therapies may have a beneficial role in the treatment of IgAN and associated proteinuria. Although previous studies have demonstrated that the administration of glucocorticoids may reduce the risk of ESRD in patients with IgAN (38,39), the optimal immunosuppressive treatment strategy for patients with IgAN who suffer with moderate to severe proteinuria remains uncertain. In the present meta-analysis, a comprehensive literature search with limited restrictions in publication language was performed in order to compare the efficacy and safety of immunosuppressive agents such as CTX, LET, MMF and AZA, which are widely used in the treatment of Chinese patients with IgAN.

A total of 1,466 patients from 29 studies (9-37) were included in the present meta-analysis. As too few studies reported long-term outcomes, the present meta-analysis only reviewed short-term parameters in order to evaluate the efficacy of the respective treatments, including the final urinary protein excretion and therapeutic remission (complete or partial) of the participants. The most frequently used definition for 'partial remission' of proteinuria was 0.3-2.0 g/day

or a decrease of 50%. Complete remission of proteinuria was defined as <0.3 g/day and serum albumin >35 g/l with normal renal function. However, these definitions may be heterogeneous.

Notably, the patients demonstrated an improved treatment response to AZA administration, as compared with steroid treatment alone (RR, 3.43; 95% CI; 1.92-6.12; P<0.0001). In addition, following treatment with MMF therapy, the Chinese patients with IgAN demonstrated significantly increased CR/PR remission rates (CR/PR; RR, 2.19; 95% CI, 1.25-3.85; P=0.006), as compared with the administration of steroid alone. In the analysis of 'LET (or plus steroid) versus steroid', the administration of LET demonstrated an improved response, as compared with steroid treatment alone. Tolerable side effects were demonstrated in patients administered AZA, MMF and LET. Only two studies involving 72 patients compared CTX plus steroid and steroid therapy alone; therefore further high quality RCTs are required in the future to determine the effects of CTX. Four studies were included in the analysis of 'CTX (or plus steroid) versus LET (or plus steroid)'; LET administration was significantly effective in inducing remission of proteinuria and was associated with a lower incidence of adverse reactions, as compared with CTX.

Some findings of the present study were consistent with the results of previous studies in patients of various ethnicities. Several RCTs have demonstrated that, when combined with steroid treatment, CTX was able to reduce urinary protein levels and conserve kidney function in patients with IgAN (19,33). Yoshikawa et al (40) demonstrated that the administration of AZA plus steroid therapy resulted in the increased complete remission of proteinuria in 80 juvenile patients newly diagnosed with IgAN. However, the efficacy of MMF administration in patients with IgAN differs among ethnicities. In a Belgian study that assessed MMF vs. placebo in 34 patients, Maes et al (41) demonstrated an average proteinuria level of 1.8 g/day; whereas no differences in the reduction of proteinuria or preservation of glomerular filtration rate were demonstrated. Similarly, in a North American study, Frisch et al (42) demonstrated that a 1-year regimen of MMF vs. placebo in patients with IgAN with an initial average proteinuria level of 2.7 g/day provided no benefits over 24 months. The efficacy and safety of LET in the treatment of patients with IgAN in other ethnicities is unknown, and no relevant RCTs were found. Due to the heterogeneity of the results from previous studies, the optimal immunosuppressive therapeutic strategy for the treatment of patients with IgAN remains controversial. The reasons for this heterogeneity require further investigation, however, the following may be considered contributing factors: Ethnicity differences; variations in the levels of therapeutic agent achieved; limited number of trials and small sample sizes; and suboptimal methodological quality. The results of the present meta-analysis demonstrated the potential of immunosuppressive agents, including AZA, CTX, MMF and LET, as a short-term (6-12 months) therapeutic strategy for the treatment of proteinuria in patients with IgAN.

The present meta-analysis had various strengths. Firstly, in an attempt to minimize bias, rigorous methods were used and only randomized trials were included. Secondly, as compared with previous meta-analyses, a greater number of studies were included and attempts were made to tabulate the occurrence of adverse events. It remains premature to recommend the routine use of AZA, CTX, MMF and LET immunosuppressive agents as treatment for patients with IgAN, for various reasons. The data analyzed in the present meta-analysis were obtained from short-term studies with small sample sizes, which were generally conducted in a single center. Furthermore, as the analysis was conducted on pooled data from published papers, individual patient and original data were not available, which prevented a more detailed analysis from being completed, which may have yielded more comprehensive results.

In conclusion, based on the Chinese patients and short duration RCTs examined, the administration of AZA, MMF, LET and CTX, demonstrated superior potency in inducing the remission of proteinuria in patients with IgAN with tolerable adverse effects, as compared with steroid treatment. In addition, as compared with CTX, LET administration demonstrated a lower incidence of adverse reactions. Furthermore, the results of the present meta-analysis support the need for a large, high-quality multicenter trial in order to ascertain whether immunosuppressive treatments may be effective in a broad population of patients with high-risk IgAN, specifically to determine their effects in kidney failure.

Acknowledgements

Note added at revision of article

Subsequently to the publication of the above article, an interested reader drew to our attention that the article described the use of the drug acetazolamide for IgA nephropathy on a number of occasions in the text, whereas the references refer to the drug azathioprine. The authors confirmed that, owing to an oversight on their part, all the references to "acetazolamide" in their paper (abbreviated as 'AZA') should have been written as "azathioprine". Given the nature of this error, note that the drug name for 'AZA' has been corrected in the article itself, and this is a revised version of the original article.

References

1. Berger J and Hinglais N: Intercapillary deposits of IgA-IgG. J Urol Nephrol (Paris) 74: 694-695, 1968 (In French).
2. Bartosik LP, Lajoie G, Sugar L and Cattran DC: Predicting progression in IgA nephropathy. Am J Kidney Dis 38: 728-735, 2001.
3. D Amico G: Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis 36: 227-237, 2000.
4. Alamartine E, Sabatier JC, Guerin C, Berliet JM and Berthoux F: Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analyses. Am J Kidney Dis 18: 12-19, 1991.

5. Bogenschütz O, Bohle A, Batz C, Wehrmann M, Pressler H, Kendziorra H and Gärtner HV: IgA nephritis: On the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. Am J Nephrol 10: 137-147, 1990.
6. Reich HN, Troyanov S, Scholey JW and Cattran DC; Toronto Glomerulonephritis Registry: Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol 18: 3177-3183, 2007.
7. Beck L, Bomback AS, Choi MJ, Holzman LB, Langford C, Mariani LH, Somers MJ, Trachtman H and Waldman M: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis. Am J Kidney Dis 62: 403-441, 2013.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ and McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 17: 1-12, 1996.
9. Huang S: Clinical observation of Benazepril combined with azathioprine on IgA nephropathy. Guo Ji Yi Yao Wei Sheng 20: 53-55, 2009.
10. Kuang B: Clinical observation of Benazepril combined with azathioprine on IgA nephropathy. ZhongGuo Xian Dai Yi Sheng 19: 6-7, 2010.
11. Li YN: Curative effect analysis of Benazepril combined with azathioprine on IgA nephropathy along with the amount of proteinuria. Hua Bei Mei Tan Yi Xue Yuan XueBao 4: 471-472, 2011.
12. Ma FL: Clinical research oil azathioprine combined with benazepril treating IgA nephropathy. Xian Dai Zhen Duan Yu Zhi Liao 6: 653-654, 2012.
13. Xu H: Azathioprine and prednisone, valsartan Clinical observation on treatment of IgA nephropathy. Zhe Jiang Yi Xue 3: 227-229, 2013.
14. Chen XM, Chen P, Cai G, Wu J, Cui Y, Zhang Y, Liu S and Tang L. A randomized control trial of mycophenolate mofeil treatment in severe IgA nephropathy. Zhonghua Yi Xue Za Zhi 82: 796-801, 2002 (In Chinese).
15. Chen XSh: Clinic Effect of Mycophenolate Mofetil combined Valsartan on IgA Nephropathy. Zhong Guo Yi Yao Zhi Nan 20: 53-54, 2010.
16. Guo QY: Efficacy of pediatric IgA nephropathy mycophenolate mofetil combined hormone therapy. Guang Dong Yi Xue 7: 902-903, 2010.
17. Huang Zh: Efficacy of focal proliferative sclerosing 38 cases of patients with IgA nephropathy. He Nan Yi Xue Yan Jiu 4: 437-439, 2012.
18. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW and Lai KN: Long-term study of mycophenolate mofetil treatment in IgA nephropathy. Kidney Int 77: 543-549, 2010.
19. Wang WM: Clinical study on treatment of IgA nephropathy with renal insufficiency by corticosteroid, corticosteroid combined with cyclophosphamide and corticosteroid combined with mycophenolate mofetil. Shang Hai Jiao Tong Da Xue Xue Bao 2: 162-167, 173, 2013.
20. Cao LO: Leflunomide in combination with medium/low dose of prednisolone in treatment of progressive IgA nephropathy. Shanghai Yi Xue 9: 791-795, 2009.
21. Fu Q: Effects of leflunomide combined with hormone therapy for lg a nephropathy. Shan Xi Yi Xue Za Zhi 3: 351-353, 2009.
22. Hu RH: IgA nephropathy leflunomide combined with hormone therapy. J Clinical Internal Medicine 12: 837-839, 2011.
23. Huang YX: Leflunomide combined small dose glucocorticoid treatment of progressive IgA nephropathy Efficacy. Chinese Journal of Primary Medicine and Pharmacy 18: 1965-1966, 2011.
24. Li T: Study on effect of leflunomide combined with glucocorticoid in treatment of progressive IgA nephropathy. Modern J Integrated Traditional Chinese and Western Medicine 1: 13-15, 2011.
25. Lou TQ: Controlled trial of leflunomide in the treatment of immunoglobulin a nephropathy. Journal of Sun Yat-sem University (Medical Sciences) 5: 570-572, 2005.
26. Pu L: Efficacy of benazepril combined with leflunomide in treatment of IgA nephropathy. Jiangsu Medical Journal 11: 1277-1279, 2012.
27. Shen P: Leflunomide combined with low-dose hormone therapy efficacy of IgA nephropathy. Chinese J General Practice 10: 1580-1581, 2012.
28. Sun MD: Clinical observation of leflunomide treatment of IgA nephropathy. Chinese J Gerontology 16: 2038-2039, 2009.
29. Wang L: Leflunomide combined with prednisone treatment of progressive IgA nephropathy Chronic. Suzhou University J Medical Science 4: 677-679, 2006.
30. Yang FY: Controlled studies of leflunomide treatment of IgA nephropathy. China Practical Medical 22: 17-19, 2009.
31. Zhang LW: Efficacy of leflunomide combined with hormone treatment of chronic progressive IgA nephropathy. Chinese Journal of Modern Drug Application 20: 116-118, 2010.
32. Zhang Y: Efficacy of leflunomide combined with prednisone in the treatment of advanced IgA nephropathy. Academic J Guangzhou Medical College 23: 82-85, 2010.
33. Liu Y: Accompanied by moderate proteinuria treatment of IgA nephropathy. China Medical Herald 6: 23-24, 2006.
34. Guo M: Compare leflunomide or cyclophosphamide combined hormone therapy of chronic progressive IgA nephropathy. Guide of China Medicine 28: 142-143, 2012.
35. Sun ZhX: Comparison of the efficacy of treatment with leflunomide and cyclophosphamide IgA nephropathy renal dysfunction. Suzhou University J Medical Science 5: 961-963, 2009.
36. Zhang HF: Leflunomide combined with glucocorticoids contrast cyclophosphamide glucocorticoid treatment efficacy of IgA nephropathy. J Taishan Medical College 6: 434-436, 2013.
37. Zhong ShH: Controlled studies of leflunomide and cyclophosphamide-based therapy to nephrotic syndrome of IgA nephropathy. J North China Coal Medical University 5: 593-594, 2011.
38. Lv J, Xu D, Perkovic V, Ma X, Johnson DW, Woodward M, Levin A, Zhang H and Wang H; TESTING Study Group: Corticosteroid therapy in IgA nephropathy. J Am Soc Nephrol 23: 1108-1116, 2012.
39. Katafuchi R, Ninomiya T, Mizumasa T, Ikeda K, Kumagai H, Nagata M and Hirakata H. The improvement of renal survival with steroid pulse therapy in IgA nephropathy. Nephrol Dial Transplant 23: 3915-3920, 2008.
40. Yoshikawa N, Honda M, Iijima K, Awazu M, Hattori S, Nakanishi K and Ito H; Japanese Pediatric IgA Nephropathy Treatment Study Group: Steroid treatment for severe childhood IgA nephropathy: A randomized, controlled trial. Clin J Am Soc Nephrol 1: 511-517, 2006.
41. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, Van Damme B and Vanrenterghem YF: Mycophenolate mofetil in IgA nephropathy: Results of a 3-year prospective placebo-controlled randomized study. Kidney Int 65: 1842-1849, 2004.
42. Frisch G, Lin J, Rosenstock J, Markowitz G, D'Agati V, Radhakrishnan J, Preddie D, Crew J, Valeri A and Appel G: Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: A double-blind randomized controlled trial. Nephrol Dial Transplant 20: 2139-2145, 2005.