Multitarget Therapy: An Effective and Safe Therapeutic Regimen for Lupus Nephritis

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ABSTRACT - Introduction: We evaluated the effectiveness and safety of various multitarget therapies for inducing remission in lupus nephritis patients. **Methods:** Randomized controlled trials (RCT) were identified and extracted from the Embase, PubMed, Chinese Biomedical Literature Database (CBM), and the Cochrane Library until Oct 31, 2018, investigations meeting inclusion criteria were extracted, and data were analyzed by meta-analysis. The total remission (TR; complete to partial remission), complete remission (CR), albumin, proteinuria levels, negative rate of anti-double-stranded DNA antibody (ds-DNA), negative rate of anti-nuclear antibody (ANA), and systemic lupus erythematosus disease activity index (SLE-DAI) were calculated using the software of RevMan 5.3. **Results:** Eleven RCTs were included and analyzed. The multitarget therapy group exhibited a higher value of CR (OR=3.06, 95%CI: 2.35-3.99, P < 0.00001) as well as TR (OR=3.83, 95%CI: 2.77-5.31, P < 0.00001) than those in the cyclophosphamide (CYC) group. In addition, multitarget therapies had more albumin (WMD=3.50, 95%CI: 1.04-5.95, P=0.005), greater albumin increases (OR=1.96, 95%CI: 0.63-3.29, P=0.004) and higher negative rates of ds-DNA (OR=2.13, 95%CI: 1.51-3.01, P < 0.0001) and ANA (OR=2.82, 95%CI: 1.77-4.50, P < 0.0001) when compared with the CYC group. This group also had less proteinuria levels (WMD=-0.55, 95%CI: -0.79 to -0.30, P < 0.0001), lower degrees of SLE-DAI (OR=-1.80, 95%CI:-2.78 to -0.81, P=0.0004), and a lower adverse reaction rate. For example, gastrointestinal syndrome, irregular menstruation and leucopenia happened less frequently in the multitarget therapy group. However, hypertension was more prevalent in the multitarget therapy group. **Conclusions:** Multitarget therapy is an effective and safe intervention for inducing remission in lupus nephritis patients.

INTRODUCTION

Lupus nephritis (LN) is the most frequent major complication in patients with systemic lupus erythematosus (SLE), and the morbidity is approximately 30%–50% in SLE patients [1, 2]. Immune activation of B cells and T helper cells can not only play a role in the pathogenesis of SLE, but also induce the inflammation, which is associated with the onset of LN [3]. B cells are also involved in T cell activation and cytokine production [4]. Persistent inflammation may induce permanent damage in the glomerulus and kidney tubules, resulting in chronic kidney disease. Without intervention, LN can develop into end stage renal disease.

Glucocorticoids (GC) plus cyclophosphamide (CYC) is the traditional therapy for LN, which is used to improve long-term prognosis of patients with LN. However, severe adverse effects are associated with this treatment, including sepsis, malignancy, hemorrhagic cystitis, and amenorrhea. In the past decades, some new immunosuppressants such as tacrolimus (TAC), cyclosporine A (CsA), mycophenolate mofetil (MMF), and leflunomide are used to treat LN.

Multitarget therapies, such as TAC plus MMF or leflunomide plus MMF, are successfully used for immunosuppression in patients with kidney transplants, and these drugs have additive inhibitory effects on lymphocytes [2]. In this study, we conducted a meta-analysis to calculate the effectiveness and safety of multitarget therapies for the induction of remission of lupus nephritis patients.

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MATERIALS AND METHODS

Search strategies for identified studies

A search strategy of Cyclophosphamide, CYC, Tacrolimus, TAC, Mycophenolate mofetil, MMF, Leflunomide, LEF, systemic lupus erythematosus and lupus nephritis, were entered into Embase, PubMed, Chinese Biomedical Literature Database (CBM), and the Cochrane Library (up to Oct 31, 2018) to identify eligible studies without language limitations. Other resources such as the references cited in articles relevant to this update were also evaluated.

Selection of studies

By reviewing the titles, abstracts, and, if necessary, the full texts, two abstractors individually screened out relevant studies. Publications were included in the analysis if patients were diagnosed as lupus nephritis by renal biopsy, and the study type was limited to randomized controlled trials. Eligibility criteria required individuals to have received different types of immunosuppressants combinations as the multitarget therapies in one arm of the treatment and CYC in the other. On the contrary, retrospective studies, one-arm studies, case reports, letters, reviews, guidelines and comments were excluded from the study. Studies with unclear diagnostic criteria for lupus nephritis in the trials were also not included. Reviewers would discuss and resolve any discordant opinions. In the analysis, only those randomized controlled trials related to the multitarget therapies for LN were included.

Outcome measures

The primary outcomes, including the effectiveness and tolerance of multitarget therapy, were assessed. The efficacy was measured by related indices such as total remission (TR; complete remission (CR) plus partial remission (PR)), CR, rise of serum albumin, decrease of urinary protein excretion, negative rate of anti-double-stranded DNA antibody (ds-DNA) and anti-nuclear antibody (ANA), systemic lupus erythematosus disease activity index (SLE-DAI). The safety of multitarget therapies was measured by adverse reaction rate and side effects such as gastrointestinal syndrome, hypertension, hyperglycemia, leucopenia, infection of various organ systems, herpes zoster or varicella, alopecia, and irregular menstruation.

STATISTICAL ANALYSIS

Review Manager Version 5.3 software was used to pool the data extracted from the individual studies. I^2 statistics was used to detect the heterogeneity. When the p-value ≥ 0.1 for the heterogeneity test, a fixed effects model was chosen for a more conservative estimate. If not, a random effects model was used to pool the results. Continuous data were presented using weighted mean differences (WMDs), and the odds ratio (OR) was used to show the binary data. 95% confidence intervals (95% CI) were assessed in the included studies. A value of $p < 0.05$ was regarded as statistical significance.

RESULTS

Search results

There were 11 randomized controlled trials [5-15] , totaling 1001 participants, of multitarget therapy for lupus nephritis in this meta-analysis, and detailed study characteristics are shown in Table 1. Of these 11 studies, 8 (n=767) compared TAC with MMF plus GC to CYC plus GC, while 3 (n=234) compared leflunomide plus MMF with or without GC to CYC with or without GC. The patients had a diagnosis of class II, III, IV, V, III+V or IV+V LN according to the ISN/RPS 2003 classification of LN.

Efficacy

Multitarget therapies versus CYC

To detect the efficacy of multitarget therapies in lupus nephritis patients, data from 11 studies [5-15] (n=1001) was used to compare multitarget therapies plus GC with CYC plus GC. Overall, there was a significant improvement in CR (P < 0.00001, OR=3.06, 95%CI: 2.35-3.99; Table 2 and Figure 1), TR (P < 0.00001, OR=3.83, 95%CI: 2.77-5.31; Table 2 and Figure 2), albumin (P=0.005, WMD=3.50, 95%CI: 1.04-5.95; Table 2), albumin increase level (P=0.004, OR=1.96, 95%CI: 0.63-3.29; Table 2), negative rate of ds-DNA (P < 0.0001, OR=2.13, 95%CI: 1.51-3.01; Table 2 and Figure 3), negative rate of ANA (P < 0.0001, OR=2.82, 95%CI: 1.77-4.50; Table 2 and Figure 4) and a significant reduction in proteinuria levels (P < 0.0001, WMD=-0.55, 95%CI: -0.79 to -0.30; Table 2), SLE-DAI (P=0.0004, OR=-1.80, 95%CI:-2.78 to -0.81; Figure 5 and Table 2) in favor of multitarget therapy.

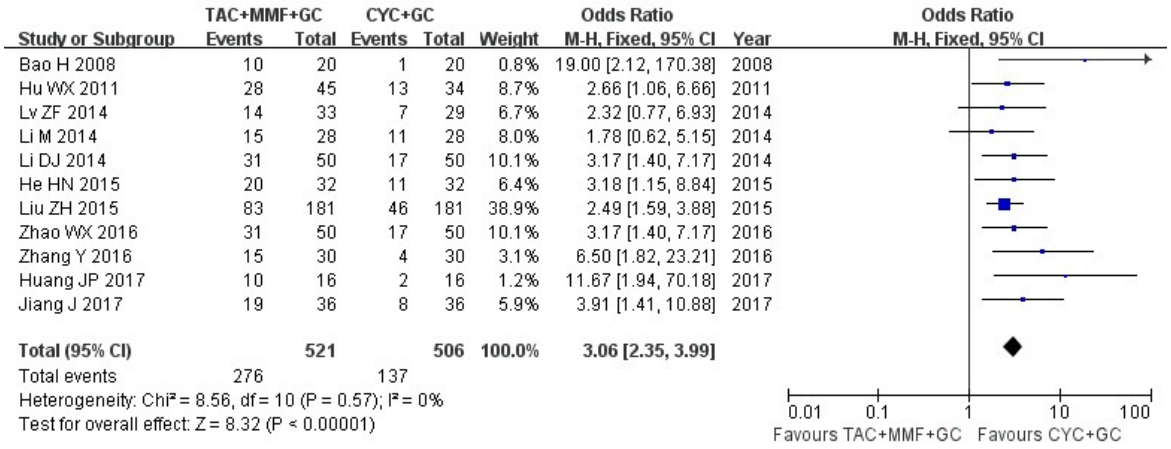

Figure 1. Assessment of the efficacy of multitarget therapy for lupus nephritis with regards to complete remission (CR).

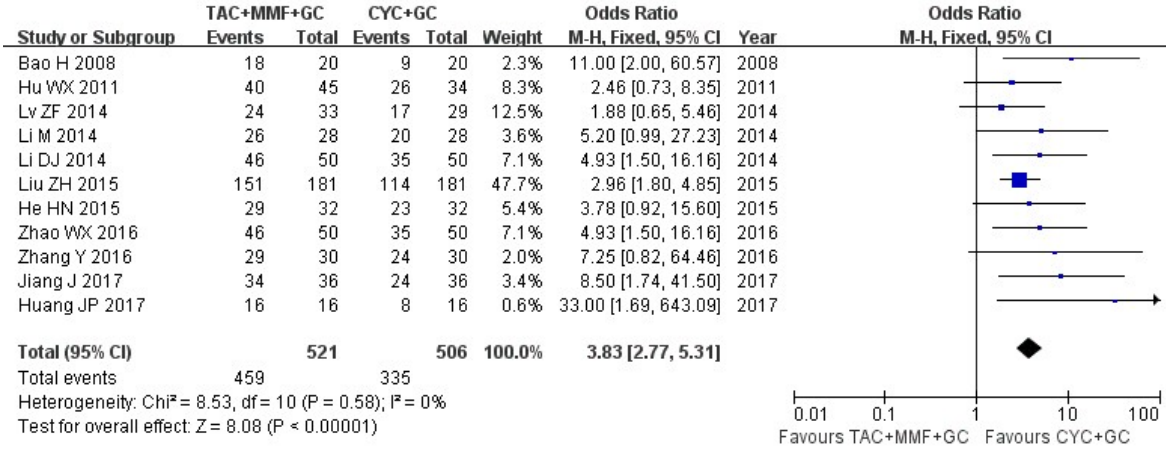

Figure 2. Assessment of the efficacy of multitarget therapy for lupus nephritis with regards to total remission (complete or partial remission) (TR).

TAC plus MMF versus CYC

Regarding the TAC+MMF vs. CYC, eight studies [5-12] including 767 patients were analyzed to determine the efficacy of TAC+MMF. TAC+MMF was superior to CYC in CR (P < 0.00001, OR=3.10, 95%CI: 2.30-4.19; Table 2), TR (P < 0.00001, OR=4.06, 95%CI: 2.80-5.89; Table 2), albumin (P < 0.00001, WMD=5.21, 95%CI: 3.44-6.98; Table 2), albumin increase level (P=0.004, OR=1.96, 95%CI: 0.63-3.29; Table 2), negative rate of ds-DNA (P=0.0004, OR=2.09, 95%CI: 1.39-3.15; Table 2), negative rate of ANA (P=0.0005, OR=3.40, 95%CI: 1.72-6.74; Table 2) and decreasing proteinuria levels (P < 0.00001, WMD=-0.61, 95%CI: -0.76 to -0.45; Table 2) and SLE-DAI (P < 0.00001, OR=-1.91, 95%CI:-2.51 to -1.30; Table 2). This result was in accordance with the overall effect of multitarget therapies compared to CYC.

Leflunomide plus MMF versus CYC

Three papers [13-15] that included 234 lupus nephritis patients were analyzed to assess the effectiveness of leflunomide +MMF. Compared with CYC, leflunomide+MMF was more effective in CR (P=0.0001, OR=2.93, 95%CI: 1.69-5.08;

Table 2) and TR (P=0.0009, OR=3.16, 95%CI: 1.60-6.23; Table 2). Significant differences were also observed in the reduction of proteinuria levels (P=0.02, WMD=-0.48, 95%CI: -0.87 to -0.09; Table 2), negative rate of ds-DNA (P=0.02, OR=2.22, 95%CI: 1.16-4.26; Table 2) and ANA (P=0.007, OR=2.39, 95%CI: 1.26-4.53; Table 2). However, leflunomide+MMF had similar effects to those of the CYC group on albumin (P=0.08, WMD=1.87, 95%CI: -0.24-3.98; Table 2) and SLE-DAI (P=0.0007, OR=-2.00, 95%CI: -3.1 to -0.85; Table 2).

Safety

Multitarget therapies versus CYC

Compared with CYC group, the multitarget therapy group had a lower rate of adverse reactions (P=0.02, OR=0.28, 95%CI: 0.01-0.81; Table 3), indicating enhanced tolerability. Specifically, the incidence rates of gastrointestinal syndrome (P=0.01, OR=0.35, 95%CI: 0.15-0.80; Table 3), leucopenia (P=0.0009, OR=0.38, 95%CI: 0.22-0.67; Table 3), irregular menstruation (P=0.01, OR=0.42, 95%CI: 0.22-0.81; Table 3) were lower in the multitarget therapy group. However, the incidence rate of hypertension in multitarget therapy group was greater than that in the CYC group. This study did not find a significant difference among the incidence rates of hyperglycemia, pneumonia, skin infection, urinary tract infection, upper respiratory infection, herpes zoster or varicella, or alopecia between the two groups (Table 3).

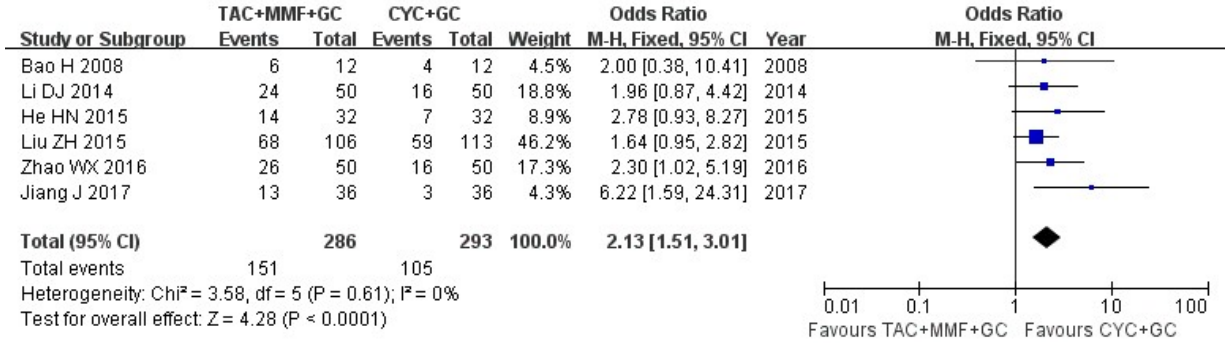

Figure 3. Assessment of the efficacy of multitarget therapy for lupus nephritis with regards to negative rates of anti-double-stranded DNA antibody (ds-DNA)

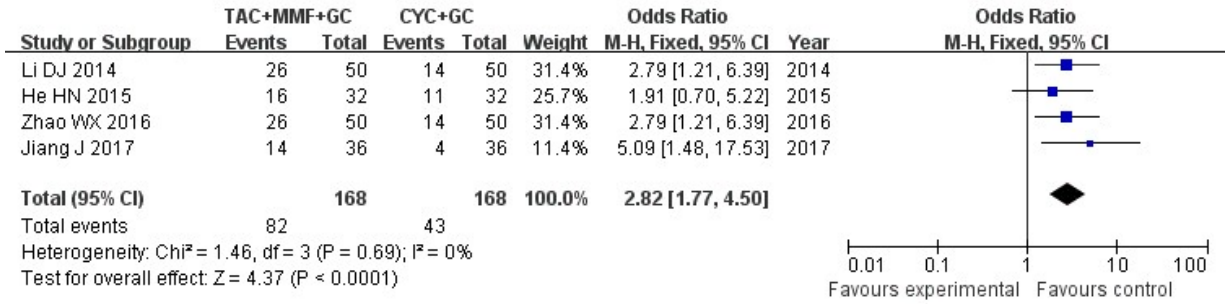

Figure 4. Assessment of the efficacy of multitarget therapy for lupus nephritis with regards to the negative rates of anti-nuclear antibody (ANA).

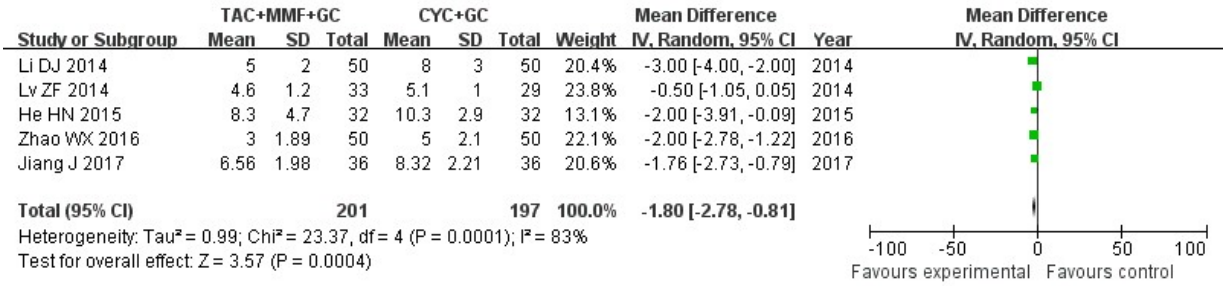

Figure 5. Assessment of the efficacy of multitarget therapy for lupus nephritis with regards to the systemic lupus erythematosus disease activity index (SLE-DAI).

DISCUSSION

In this meta-analysis, we assessed the effectiveness and safety of multitarget therapies in inducing remission in lupus nephritis patients. The results indicate that multitarget therapies can result in superior rates of TR, and CR, decreased rates of ds-DNA and ANA, and low proteinuria levels. The safety of multitarget therapy was also assessed, and the results indicated that the multitarget therapy group exhibited lower adverse reaction rates than that the CYC group. Adverse events including leucopenia, gastrointestinal syndrome and irregular menstruation were less prevalent in the multitarget therapy group. These results indicate that multitarget therapy is an effective and safe treatment for lupus nephritis patients.

In the sub-group analysis, the multitarget therapy regimen of TAC+MMF had greater values for TR, CR, albumin, and albumin increase, and decreased levels of ds-DNA, ANA, proteinuria and SLE-DAI compared to CYC. There were eight RCTs included for this meta-analysis. Furthermore, the comparison of the multitarget therapy regimen of leflunomide +MMF with CYC indicated that the multitarget therapy group had greater of TR and CR, and decreased levels of ds-DNA, ANA, proteinuria. There were only three RCTs included for this meta-analysis, and additional studies are needed to confirm these findings.

In a previous study, Deng et al [16] performed a meta-analysis and reported that multitarget therapy is more effective at inducing CR compared with CYC, and the rates of irregular menstruation, leukopenia, gastrointestinal symptoms and were significantly reduced in the multitarget therapy group compared with the CYC group. However, the multitarget therapy group exhibited a higher prevalence of new-onset hypertension than the CYC group. Our meta-analysis had similar results, and we also included a meta-analysis of leflunomide +MMF vs. CYC.

In the current meta-analysis, the results indicate that multitarget therapy is a valid therapeutic option for inducing remission in lupus nephritis patients. Additional RCTs are needed to confirm the effectiveness and safety of multitarget therapies for LN.

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Table 1. Characteristics of the studies included in this meta-analysis.

Ref	Design	Treatment	Details	Patients	Main outcome	Adverse events
5	Multicenter,randomized, open-label, clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC 3-4mg/day; TAC blood concentration within 5-7ng/m; MMF 0.75-1g/day; MPA AUC (0-12h), 20-45 mg h/L. C: IVC 0.5-1g/m^2per month for 6-9 months. All MP pulse therapy followed by oral prednisone	12- 60 yr; Class V+IV LN	CR, TR, urinary protein decline, rise of serum albumin, negative rate of ds-DNA	Gastrointestinal syndrome, leucopenia, hypertension, hyperglycemia, upper respiratory infection, pneumonia, herpes zoster or varicella, urinary tract infection, alopecia, irregular menstruation
10	Multicenter,randomized, open-label, clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC 4 mg/day, MMF 1g/day C: IVC 0.5-1 g/m^2 monthly for 24 weeks. All MP pulse therapy followed by oral prednisone	18-65 yr biopsy-proven LN diagnosed within 6 months before enrollment; had a diagnosis of class III, IV, V, III+V or IV+V LN	CR, TR, urinary protein decline, rise of serum albumin, negative rate of ds-DNA	Gastrointestinal syndrome, leucopenia, hypertension, hyperglycemia, upper respiratory infection, pneumonia, herpes zoster or varicella, urinary tract infection, alopecia, irregular menstruation
7	Randomized clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC (3-4mg/day), maintain a blood concentration within 10 ng/mL, MMF (0.75-1g/day), maintain AUC from 0 to 12 h of MPA within 45 mg h/L. C: IVC 0.5-1 g/m^2 monthly for 6 months. All patients received MP pulse therapy	18-60 yr biopsy-proven LN diagnosed within 6 months; had a diagnosis of class III, IV, V, III+V, and IV+V LN	CR, TR, proteinuria levels, albumin, SLE-DAI, negative rate of ds-DNA	Cytomegalovirus infection, fungal infection, bacterial infection, skin infection, lung infection, gastrointestinal symptoms, urinary system infection, leukopenia
11	Randomized clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC (2-4mg/day), MMF (0.5-1 g/day). C: IVC 8-12 mg/kg per month for 24 weeks. All patients received MP pulse therapy followed by oral prednisone	Biopsy-proven LN had a diagnosis of class IV LN	CR, TR	Hypertension
9	Randomized clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC 4 mg/day, MMF 1 g/day. C: IVC 0.75 g/m^2 to maximum of less than 1.2g per month for 6-9 months. All received MP pulse therapy followed by oral prednisone	Biopsy-proven LN had a diagnosis of class IV, III+V, and IV+V LN	CR, TR	Gastrointestinal syndrome, leucopenia, hypertension, herpes zoster or varicella, irregular menstruation, adverse reaction rate
6	Randomized clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC 4 mg/day, blood concentration within 4-7 ng/mL, MMF 1g/day; AUC from 0 to 12 h of MPA at 20-30 mg h/L. C: IVC 0.5-1 g/m2 monthly for 6-9 months. All received MP pulse therapy followed by oral prednisone	Biopsy-proven LN had a diagnosis of class IV, III+V, and IV+V LN	CR, TR	Gastrointestinal syndrome, leucopenia, hypertension, hyperglycemia, Pneumonia, herpes zoster or varicella, skin infection, irregular menstruation, adverse reaction rate

12	Randomized clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC 0.15mg/kg daily, MMF 50 mg/kg daily. C: IVC 0.8-1 g monthly for 9 months. All received MP pulse therapy followed by oral prednisone	Biopsy-proven LN had a diagnosis of class II, III, IV, III+V, and IV+V LN	CR, TR, negative rate of ds-DNA, negative rate of ANA, proteinuria levels, albumin, SLE-DAI	Gastrointestinal syndrome, leucopenia, alopecia, irregular menstruation
8	Randomized clinical trial	TAC+MMF+GC vs CYC+GC	M: TAC (3-4mg/day); blood concentration within 10 ng/mL, MMF (0.75-1 g/day), maintain AUC(0-12h) of MPA within 45 mg h/L. C: IVC 0.5-1g/m^2 monthly for 6 months. All received MP pulse therapy followed by oral prednisone	Biopsy-proven LN had a diagnosis of class III, IV, V LN	CR, TR, negative rate of ds-DNA, negative rate of ANA, proteinuria levels, albumin, SLE-DAI	Gastrointestinal syndrome, leucopenia, alopecia
13	Randomized clinical trial	LEF+MMF vs CYC	M: LEF 20mg/day for 3 months, stepping by LEF 10mg/day for 6 months; at the same time, MMF 250mg bid for 9 months. C: IVC 0.8-1.0g 2 times / month, 2 months later 1 time / month for 9 months	Biopsy-proven LN had a diagnosis of class II, III, IV, III+V, and IV+V LN	CR, TR, negative rate of ds-DNA, negative rate of ANA, proteinuria levels, albumin, SLE-DAI	Gastrointestinal syndrome, leucopenia, skin infection, irregular menstruation, adverse reaction rate
14	Randomized clinical trial	LEF+MMF+GC vs CYC+GC	M: LEF 20mg/day for 3 months, LEF 10mg/day for 6 months; at the same time, MMF 250mg bid for 9 months. Furthermore, At the same time oral prednisone (0.8-1.0 mg / kg, gradually reduced to 6 -10 mg / day after 6 weeks). C: IVC 0.8-1.0g once/month for 9 months. All received oral prednisone	NS	CR, TR, negative rate of ds-DNA, negative rate of ANA, proteinuria levels, albumin, SLE-DAI	Gastrointestinal syndrome, leucopenia, alopecia, irregular menstruation, adverse reaction rate
15	Randomized clinical trial	LEF+MMF+GC vs CYC+GC	M: combining LEF 10mg qd and MMF 1g qd for 6 months. C: IVC 0.5-1.0g/m^2 once/month for 6 months. All the patients from two groups were treated with GC. MP 500mg/day for 3 days +	Biopsy-proven LN had a diagnosis of class II, III, IV, III+V, and IV+V LN	CR, TR, negative rate of ds-DNA, negative rate of ANA, proteinuria levels, SLE-DAI	Gastrointestinal syndrome, upper respiratory infection, herpes zoster or varicella, irregular menstruation, adverse reaction rate

			oral prednisone 0.5mg/kg.d. After 4 weeks of oral administration, the reduction is 10%-20% to 5-7.5 mg/d every 1-2 weeks			

Abbreviations: TAC: tacrolimus; GC: glucocorticoids; CYC: cyclophosphamide; LEF: leflunomide; MMF: mycophenolate mofetil; MP: methylprednisolone; AUC: area under the curve; MPA: mycophenolic acid; IVC: intravenous cyclophosphamide; CR: complete remission; TR: total remission (complete or partial remission); ANA: antinuclear antibody; ds-DNA: anti-double-stranded DNA antibody; SLE-DAI: systemic lupus erythematosus disease activity index; LN: lupus nephritis; ISN: international society of nephrology; RPS: renal pathology society; qd: once a day; bid: twice a day; M: multitarget therapy group; C: control group; NS: Not shown.

Table 2. Meta-analysis of the efficacy of multitarget therapy in induction therapy of patients with lupus nephritis

Therapeutic regimen	Indicators	Studies Number	Q test *P*-value	Model selected	OR/WMD (95%CI)	P
Multitarget Therapy+GC vs. CYC+GC	CR	11	0.57	Fixed	3.06 (2.35, 3.99)	< 0.00001
	TR	11	0.58	Fixed	3.83 (2.77, 5.31)	< 0.00001
	Proteinuria levels	5	0.008	Random	-0.55 (-0.79, -0.30)	< 0.0001
	Albumin	4	0.0002	Random	3.50 (1.04, 5.95)	0.005
	Albumin rise level	2	0.25	Fixed	1.96 (0.63, 3.29)	0.004
	Negative rate of ds-DNA	6	0.61	Fixed	2.13 (1.51, 3.01)	< 0.0001
	Negative rate of ANA	4	0.69	Fixed	2.82 (1.77, 4.50)	< 0.0001
	SLE-DAI	5	0.0001	Random	-1.80 (-2.78,-0.81)	0.0004
TAC+MMF+GC vs. CYC+GC	CR	8	0.31	Fixed	3.10 (2.30,4.19)	< 0.00001
	TR	8	0.46	Fixed	4.06 (2.80,5.89)	< 0.00001
	Proteinuria levels	2	0.37	Fixed	-0.61 (-0.76, -0.45)	< 0.00001
	Albumin	2	0.65	Fixed	5.21 (3.44, 6.98)	< 0.00001
	Albumin rise level	2	0.25	Fixed	1.96 (0.63, 3.29)	0.004
	Negative rate of ds-DNA	4	0.35	Fixed	2.09 (1.39, 3.15)	0.0004
	Negative rate of ANA	2	0.43	Fixed	3.40 (1.72, 6.74)	0.0005
	SLE-DAI	2	0.71	Fixed	-1.91 (-2.51,-1.30)	< 0.00001
LEF+MMF+GC vs CYC+GC	CR	3	0.89	Fixed	2.93 (1.69, 5.08)	0.0001
	TR	3	0.47	Fixed	3.16 (1.60, 6.23)	0.0009
	Proteinuria levels	3	0.04	Random	-0.48(-0.87, -0.09)	0.02
	Albumin	2	0.06	Random	1.87 (-0.24, 3.98)	0.08
	Negative rate of ds-DNA	2	0.62	Fixed	2.22 (1.16, 4.26)	0.02
	Negative rate of ANA	2	0.57	Fixed	2.39 (1.26, 4.53)	0.007
	SLE-DAI	3	< 0.0001	Random	-1.79 (-3.64, 0.07)	0.06

Abbreviations: TAC, tacrolimus; GC, glucocorticoids; MMF, mycophenolate mofetil; LEF: leflunomide; CYC, cyclophosphamide; CR, complete remission; TR, total remission, complete plus partial remission; SLE-DAI, systemic lupus erythematosus disease activity index; OR: odds ratio; WMD, weighted mean difference; CI: confidence intervals.

Table 3. Meta-analysis of the safety of multitarget therapy in induction therapy of patients with lupus nephritis

Indicators	Studies Number	Q test *P*-value	Model selected	OR (95%CI)	P
Gastrointestinal syndrome	10	0.006	Random	0.35 (0.15, 0.80)	0.01
Leucopenia	9	0.40	Fixed	0.38 (0.22, 0.67)	0.0009
Hypertension	5	0.87	Fixed	3.34 (1.44, 7.75)	0.005
Hyperglycemia	3	0.54	Fixed	1.09 (0.38, 3.14)	0.88
Skin infection	3	0.87	Fixed	0.67 (0.17, 2.59)	0.56
Upper respiratory infection	3	0.16	Fixed	0.78 (0.45, 1.34)	0.36
Pneumonia	4	0.70	Fixed	1.65 (0.71, 3.84)	0.25
Herpes zoster or varicella	5	0.52	Fixed	1.71 (0.79, 3.72)	0.17
Urinary tract infection	3	0.92	Fixed	0.71 (0.22, 2.27)	0.56
Alopecia	6	0.81	Fixed	0.55 (0.28, 1.08)	0.08
Irregular menstruation	8	0.88	Fixed	0.42 (0.22, 0.81)	0.01
Adverse reaction rate	6	0.0001	Random	0.28 (0.10, 0.81)	0.02

Abbreviations: OR: odds ratio; CI: confidence intervals.