REVIEW ARTICLE

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Rituximab treatment for lupus nephritis: A systematic review

Abstract

Purpose: We used the Cochrane systematic review to analyze the effectiveness and safety of rituximab for lupus nephritis.

Methods: Systematic search was performed among Cochrane clinical controlled trials database, MEDLINE, MEDLINE-IN-Process and Other Non-Indexed Citations, EMBASE, EBSCO CINAHL, CNKI, VIP and Wanfang database from the establishment of the database to February 2016. The effectiveness and safety were evaluated in terms of the complete remission rate, total remission rate, urinary protein, Systemic Lupus Erythematosus Disease Activity Index changes and adverse events rate. Data were analyzed by the Review Manager Software version 5.3.

Results: Five RCTs that met the inclusion criteria, including a total of 238 patients, were enrolled in our study. The results showed that the complete remission rate in rituximab group was a significantly higher than that of cyclophosphamide group. The difference between the two groups was statistically significant (OR=2.80, 95%CI(1.08,7.26), $P=0.03$). But there was no significant difference between the two groups in partial and total remission rate. The complete remission rate, partial remission rate and total remission rate in rituximab treatment group was similar compared with mycophenolate mofetil group and rituximab combined with cyclophosphamide group. The adverse reaction rate was also similar among the groups.

Conclusions: The study systematically analyzed the effectiveness and safety of rituximab for lupus nephritis, which suggested that the complete remission rate of rituximab in the treatment of lupus nephritis was a significantly higher than that of cyclophosphamide group, while the effectiveness and safety was of no difference compared with cyclophosphamide and mycophenolate mofetil.

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Introduction

Glucocorticoid, combined with an immunosuppressant, has been considered the standard treatment option for lupus nephritis (LN) [1]. However, treatment effectiveness was poor in some of the patients. Rituximab (RTX) is a human-mouse chimeric monoclonal antibody. Clinical research from China and abroad has verified the effectiveness and safety of rituximab in the treatment of LN [2-20]. The international guidelines recommended RTX in the treatment of LN; however, there is a lack of evidence-based evidence. The purpose of this study is to use a Cochrane systematic review to collect data on randomized control trials (RCTs) for the treatment of LN and then to analyze and discuss the difference in effectiveness and safety between RTX and other therapies.

Materials and methods

Search method

Prospective or randomized clinical trials were searched from EBSCO CINAHL, Ovid MEDLINE, Ovid MEDLINE-In-Process & Other Non-Indexed Citations, Ovid EMBASE, CENTRAL database, CNKI and Wanfang, Weipu databases were searched from the establishment of the database to February 2016. The keywords/phrases used were "rituximab," "CD20," and "lupus nephritis." We searched through the combination of keywords and titles. The search was free of limited language, date and publication status.

Inclusion criteria

Prospective trials or RCTs of rituximab treatment for LN were included in this study. The experimental group was RTX only or RTX combined with glucocorticoid. The control group was mycophenolate mofetil (MMF) only, cyclophosphamide (CTX) only, placebo or these medications combined with glucocorticoid.

Exclusion criteria

The patients with other secondary renal diseases were excluded from our analysis. Non-controlled studies or case reports were also excluded.

Data extraction

Two evaluators screened all the titles and abstracts according to the inclusion criteria and excluded irrelevant references. All possible RCTs, which might be consistent with the inclusion criteria, were selected and read to make sure if they completely met the criteria. The data extracted included sample size, baseline level, RTX course of treatment,

complete remission rate, partial remission rate and total remission rate, serum albumin, hemoglobin, urinary protein, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and adverse events. If the two evaluators disagreed on any included or excluded research, they discussed with each other or the third evaluator was invited. Patients are excluded if they were younger than or equal to 18 years of age.

Quality assessment

The Cochrane Collaboration's tool for assessing risk bias was used to assess the risk bias of the enrolled RCT, which included random number generation method, allocation concealment, blind method, incomplete results, selected result report and other biases (e.g., unbalanced underlying diseases and different study designs). The PRISMA quality evaluation system was used to assess the quality of the literature.

Statistical analysis

The data were analyzed by Revman 5.3.5 software provided by Cochrane Collaboration. We analyzed the clinical heterogeneity and methodological heterogeneity of the enrolled studies, followed by a subgroup analysis of the enrolled studies according to the origin of heterogeneity. The X^2 test was used to detect the statistical heterogeneity and I^2 test was to detect heterogeneity size. If there was no statistical heterogeneity between the studies ($p > 0.1$ or $I^2 < 50\%$), a fixed effect model was used. If there was statistical heterogeneity between the studies ($p < 0.1$ or $I^2 > 50\%$), a randomized effect model and subgroup analysis were used to analyze the origin of the heterogeneity. Quantitative data were used to calculate mean difference (MD) and 95%

FIGURE 1. Process of screening the literature

confidence interval (CI). Categorical data were used to calculate relative risk (RR) and 95% CI. For studies with insufficient combined effect size, qualitative systematic review was used.

Results

Searching results

One hundred sixty-one studies were retrieved from database and manual searches, and 139 patients were enrolled (after

excluding duplicates and those who did not meet the inclusion criteria). Five studies which met the inclusion criteria were finally selected [21-25] (Figure 1). Moroni [21] divided the control group into two groups, while other studies had only one group for the control group. The essential characteristics of the enrolled studies were shown in Table 1.

TABLE 1. Descriptions of the enrolled studies

Study author (year)	Intervention			Average age/ year	Base-line	Pathology type	Course of treatment	Outcome
	Treatment (F/M)	Control (F/M)	Other drugs					
Yi (2014)	RTX:12,(10/2)	CTX:15,(12/3)	-	RTX:33.4 CTX:38.2	Similar	RTX: IV+V4; III+V8	6 months	a-i
	17~63	15~50				CTX: IV+V5;III+V10		
Rovin (2012)	RTX+MMF:72 (67/5)	Placebo+MMF: 72 (63/9)	-	35.50±6.29	Similar	RTX:24/48/8/15* placebo:25/47/18/28*	78 weeks	a,b,f,g,j
Li (2009)	RTX:9(9/0)	RTX+CTX:10(9/1)	-	32.50±8.57	Similar	RTX:1/1/7/0*		a-d,f,g,j-l
						RTX+CTX:1/2/6/1*		
Moroni (2014)	RTX:17(15/2)	MMF:17(15/2)	CTX:20(17/3)	31.4±11.3	Similar	RTX: 1/11/1/0/4†	12 months	c-g,j,l
						MMF: 4/7/1/2/0†		
Moroni (2012)	RTX:10(10/0)	CTX:14(13/1)	-	RTX:31.4 CTX:35.2	Similar	CTX:4/8/0/2/6†	12 months	a-g,j
						RTX:0/8/0/2* CTX:3/8/1/2*		

Abbreviations: CTX, cyclophosphamide; MMF, mycophenolate mofetil; RTX, rituximab

Outcomes: a: complete remission rate; b: total remission rate; c: urinary protein; d: serum protein level; e: SLEDAI; f: C3; g: C4; h: CD19+; i: B cell; j:antinuclear antibodies; k: creatinine clearance rate; andl: serum creatinine.

The class of renal pathology: (I) renal response at 3 months: improvement of serum creatinine if impaired at baseline and reduction of 50% of proteinuria and of microscopic hematuria; (II) complete renal remission at 12 months: serum creatinine <1.2 mg/dL (or return to the baseline value in patients with chronic renal dysfunction) and proteinuria <0.5 g/24 h and <5 urinary erythrocytes/high power field (HPF); (III) partial renal remission at 12 months: serum creatinine <1.2 mg/dL (or return to the baseline value in patients with chronic renal dysfunction) and proteinuria of 0.5-2 g/day; (IV) no response: no improvement in proteinuria or in serum creatinine if impaired at baseline; (v) acute renal dysfunction: increase of serum creatinine to >1.2 mg/dL and creatinine clearance<75 ml/min; and (VI) chronic renal insufficiency: doubling of plasma creatinine lasting for at least 6 months with a value of plasma creatinine >2 mg/dL and creatinine clearance <40 ml/min without any improvement over time.

*: III/IV/V+III/V+IV

†: III/IV/V/V+III/V+IV

TABLE 2. PRISMA Report Quality Evaluation Results

Section and topic	Item	Checklist item	Yes (%)	No (%)
Title				
Identification	1a	Identify the report as a protocol of a systematic review	5 (100.00)	0 (0.00)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	5 (100.00)	0 (0.00)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5 (100.00)	0 (0.00)
Authors				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	5 (100.00)	0 (0.00)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	5 (100.00)	0 (0.00)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	5 (100.00)	0 (0.00)
Support				
Sources	5a	Indicate sources of financial or other support for the review	4 (80.00)	1 (20.00)
Sponsor	5b	Provide name for the review funder and/or sponsor	4 (80.00)	1 (20.00)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	5 (100.00)	0 (0.00)
Introduction				
Rationale	6	Describe the rationale for the review in the context of what is already known	0 (0.00)	5 (100.00)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5 (100.00)	0 (0.00)
Methods				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4 (80.00)	1 (20.00)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	3 (60.00)	2 (40.00)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 (100.00)	0 (0.00)
Study records				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	3 (60.00)	2 (40.00)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5 (100.00)	0 (0.00)

Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5 (100.00)	0 (0.00)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4 (80.00)	1 (20.00)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4 (80.00)	1 (20.00)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5 (100.00)	0 (0.00)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5 (100.00)	0 (0.00)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	5 (100.00)	0 (0.00)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	4 (80.00)	1 (20.00)

Quality of the studies

Cochrane collaboration risk bias assessment tool was used to assess bias from six aspects: YES, which indicated a low risk of bias; NO, which indicated a high risk of preference; UNCLEAR, which indicated that the situation was not certain. The assessment of bias risk is presented in Figure 2. The PRISMA literature quality evaluation of related literatures is shown in Table 2.

Comparison of RTX and CTX in the treatment of LN

Three studies [21-23] reported a comparison of remission rate for RTX and CTX in the treatment of LN. A total of 88 patients were enrolled; 39 were in the RTX group and 49 were in the CTX group. Meta-analysis showed that there was a significant difference between the two groups (OR=2.80, 95%CI(1.08,7.26), $P=0.03$) and the remission rate of the RTX group was significantly better than that of the CTX group (Figure 3).

Morini [22] found that in the RTX group, 90% of patients had urinary protein levels lower than 0.5 g/day, while in CTX group, only 71% of patients had urinary protein lower than 0.5 g/day. Moroni [21] showed that the observed values in the two groups within 12 months were significantly different compared with baseline data ($p<0.01$). Yi [23] suggested that the observed values in the two groups within six months within ($p<0.01$) and between ($p<0.05$) the two groups were significantly different compared with baseline data.

Morini [22] found that the average baseline levels of hemoglobin in RTX and CTX was 10.9 g/L and 11.1 g/L. After 12 months, the average baseline levels of hemoglobin in the two groups was 12.1 g/L and 12.4 g/L. Moroni [21] showed that in RTX group there was no statistically difference compared with the baseline level at 12 months ($p=0.7$), while in CTX group there was a significant difference ($p=0.02$). Yi [23] found that the average baseline levels of hemoglobin in RTX and CTX group were significantly different ($p<0.05$).

Morini [22] suggested that there was a significant difference of SLEDAI decrease in the two groups. Moroni [21] and Yi [23] showed that there was a significant difference of SLEDAI compared with baseline level in and between the two groups.

There was low possibility of adverse effects, of which infection was relatively common. Some rare cases showed allergies and amenorrhea. Yi [23] showed that there were 12 adverse effect cases in CTX group (three were respiratory infection, three were upper gastric syndromes and six were other adverse effects) and five adverse effect cases in RTX group (two were respiratory infection and three were upper gastric syndromes), but there was no significant difference between the two groups. Other two studies did not compare the adverse effect.

Comparison of RTX and MMF in the treatment of LN

Two open clinical trials [21, 22] compared the efficiency and safety of RTX and MMF in the treatment of LN. There

FIGURE 2. Constitution diagram of risk bias assessment of the enrolled studies

were a total of 178 patients in the studies, among which 89 were in RTX group and 89 were in MMF group. There were no significant differences in complete remission rate and overall efficient rate in RTX and MMF groups at the end of the study (52 weeks).

Morini [22] found after 12 months of treatment, serum albumin in RTX group was higher than 3.5 g/dL in all patients while there were 3 patients had serum albumin lower than 3.5 g/dL in MMF group. There was no a significant difference in the two groups.

No significant difference was observed in SLEDAI for RTX and MMF groups compared with baseline results.

Morini [22] found that one patient exhibited an allergic reaction and two patients exhibited mild infection in the RTX group. In MMF group, three patients exhibited diarrhea (among which one was hypoleucocytosis), one patient had pneumonia and nasitis and one patient had a *Varicella-zoster virus* infection. Rovin reported that there were 72 adverse events in the RTX group and 68 in the placebo group. The most common adverse effects were hypertension, dyspepsia, nausea, headache, diarrhea and dysgeusia.

FIGURE 3. Forest plot of the complete remission rate of rituximab (RTX) vs. cyclophosphamide (CTX) in the treatment of lupus nephritis

Comparison of RTX and RTX combine with CTX in the treatment of LN

One randomized clinical trial [25] compared the efficacy and safety of rituximab and rituximab combined with CTX (RTX+CTX) in the treatment of LN. There was no statistical difference between the two groups in terms of complete and partial remission rates. There was a significant difference between the two groups in secondary endpoint events (proteinuria, serum albumin level, antinuclear factor and SLEDAI) of the two groups in the 48-week follow-up period ($p < 0.001$). Twelve people presented with infection and there was no a significant difference in the two groups with respect to infection.

Discussion

This meta-analysis included a total of five clinical studies. Our analysis showed that the complete and partial response rates of LN treatment in the RTX group were significantly higher than in the CTX group. However, we also observed that RTX showed little advantage compared with the classic immunosuppressants tested.

There are many factors that can affect the final outcome of this analysis, such as the design of the studies, the clinical course of the patients, the type of pathologies, the follow-up times, ages, ethnicities and follow-up periods. More high-quality RCTs are needed to verify these results.

In Yi's study, the complete remission rate in the RTX group was significantly higher than that of the CTX group, as evidenced by a decrease in the 24 h urinary protein values and SLEDAI. These enrolled participants had refractory severe LN, with pathology type III+V or type IV+V. In two other studies, the patients also included some non-refractory LN, which suggested that RTX might have a significant effect on refractory LN. Looney et al. [26] suggested that RTX could relieve the symptoms of most refractory severe SLE patients. Ramos et al. [27] found that RTX significantly improved the symptoms of 91% of refractory and recurrent LN patients. Studies from China and abroad also suggested that CD20 monoclonal antibody was effective for refractory severe SLE.

Our study has several limitations. First, we included some literature without careful statistical descriptions and without detailed result shift analysis. Secondly, there were some differences in 1) the case standards and 2) the pathological classification standards in the studies. These differences reduce the consistency of the results. Finally, this study did not focus on the treatment of pediatric lupus nephritis, nor did it full discuss some cases with clinical

complications. So caution should be used when considering the clinical applicability of these analyses.

Conclusion

This study showed that RTX was superior to CTX in the treatment of LN in terms of total remission rate, and that RTX was similar to mycophenolate mofetil in the treatment of LN in terms of efficacy and safety.

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