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Research Article

Comparison between Rituximab and Cyclophosphamide in Treatment of ANCA-Associated Vasculitis on Remission Induction: A Meta-Analysis

Wang K[1], Chen Y[1] and Xu J[2]*

[1]College of Clinical Medicine of Henan University of Science and Technology, Luoyang, Henan, China

[2]Department of Endocrinology and Metabolism, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, Henan, China

***Corresponding author:** Jiayun Xu, Department of Endocrinology and Metabolism, the First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471000, Henan, China

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Abstract

Objectives: Currently, immunosuppressants including cyclophosphamide and azathioprine are the main treatment options for anti-neutrophil associated vasculitis. However, since cyclophosphamide may cause serious adverse reactions, it is necessary to explore for a new drug, and rituximab is one option with less adverse reaction. There are a few studies on rituximab versus cyclophosphamide in the treatment of antineutrophil associated vasculitis. The meta-analysis is carried out to evaluate the efficacy of rituximab, compared with cyclophosphamide, as a remission induction therapy in AAV.

Methods: Firstly we searched a Chinese database (CNKI, Wanfang) and English databases (Pubmed, Cochrane Library, Embase) according to inclusion criteria and exclusion criteria before October, 2021. Then Revman5.4 and Stata were used for data analysis which was then integrated by fixed effects or random effects.

Results: After browsing the full texts, we finally included 7 eligible articles, involving 737 patients in total. With Revman5.4 software, we could draw the following conclusions: 6-month complete response rate (Chi^2=0.46, df=1 P=0.50 I^2=0%), 12-month complete response rate (Chi^2=0.31 df=1 P=0.58 I^2=0%), 18-month complete response rate (Chi^2=0.18 df=1 P=0.67 I^2=0%). Adverse event (Chi^2=3.15 df=4 P=0.53 I^2=0%), respectively for reached primary endpoint, failed primary endpoint in contrast. The result showed (Chi^2=3.29 df=3 P=0.35 I^2=9%, Chi^2=1.72 df=2 P=0.42 I^2=0%), 6-momth relapse, 12-momth relapse, 18-month relapse (Chi^2=0.22 df=1 P=0.64 I^2=0%, Chi^2=0.04 df=2 P=0.98 I^2=0%, Chi^2=0.13 df=1 P=0.72 I^2=0%), GPA 0f 6-month (Chi^2=0.47 df=1 P=0.50 I^2=0%), MPA of 6-month (Chi^2=1.52 df=1 P=0.22 I^2=34%). The above data are statistically significant.

Conclusion: Based on the above data, we can conclude that compared with cyclophosphamide, rituximab can play a certain role in the treatment of ANCA disease, improve the complete response rate, reduce the rate of adverse reactions and recurrence, and is expected to replace cyclophosphamide as a first-line drug in clinical practice.

Keywords: Rituximab; Cyclophosphamide; ANCA-Associated Vasculitis; Remission induction; Meta-analysis

Introduction

ANCA-associated vasculitis is a group of systemic small vasculitis characterized by the detection of ANCA in serum, mainly involving small blood vessels (arterioles, arterioles, venules, and capillaries) and middle and small arteries as well. Including microscopic polyvasculitis, granulomatous polyvasculitis and eosinophilic granulomatous polyvasculitis are mainly related to genetic factors and infection, especially bacterial infection and morbidity. The pathological changes are characterized by full-thickness inflammation and necrosis of small blood vessels with or without granulomatous formation. Close attention shall be paid to cellulate-like necrosis and infiltration of neutrophils, lymphocytes, and eosinophils. The treatment of ANCA-related vasculitis can be divided into two stages: induced remission and maintenance remission. The induced remission is usually sufficient glucocorticoid, combined with immunosuppressive therapy, CTX is most commonly used, and the maintenance remission is mainly low-dose glucocorticoid, combined with immunosuppressive therapy, such as azathioprine and methotrexate.

Cyclophosphamide (CYC) has been widely used in induction therapy for AAV for decades with a remission rate of 70-90% [1,2]. However, CYC leads to many serious acute side effects, such as haemorrhagic cystitis, tumors of the urinary bladder, infertility, and bone marrow depression [3]. Therefore, it is necessary to explore for new agents with similar efficacy but less toxicity.

Rituximab is a B-cell-depleting anti-CD20 monoclonal antibody that has been approved by the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of non-

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Hodgkin's lymphoma [4] and rheumatoid arthritis [5-8]. In ANCA-associated vasculitis, B-cell activation and levels of B-cell-activating factor correlate with disease activity [9,10]. Cyclophosphamide suppresses the activation, proliferation, and differentiation of autoreactive B cells [11]. The pathogenic role of B-cells and ANCA in ANCA-associated vasculitis supports B-cell-targeted therapy.

At present, it is believed that rituximab has the same effect as cyclophosphamide are the same. A meta-analysis is made in this paper based on the synthesis of all the studies.

Materials and Methods

We conducted a meta-analysis with the methods specified in the Cochrane Handbook for Systematic Reviews of Intervention [12]. Pubmed, Embase, Cochrane Library, CNKI and Wanfang database were used to retrieve articles with subject words and free words. The deadline was October, 2021. Medical Subject Headings (Mesh) terms or free text are used as follows: "rituximab" or "CD20 Antibody, Rituximab" or "Rituximab CD20 Antibody" or "Mabthera" or "IDEC-C2B8 Antibody" or "IDEC C2B8 Antibody" or "IDEC-C2B8" or "IDEC C2B8" or "GP2013" or "Rituxan" and "ANCA - Associated Vasculitis" or Anti Neutrophil Cytoplasmic Antibody Associated Vasculitis or ANCA-Associated Vasculitis or ANCA Associated Vasculitis or Vasculitis, ANCA-Associated or Pauci-Immune Vasculitis or Pauci Immune Vasculitis or Pauci-Immune Vasculitides or Vasculitides, Pauci-Immune or Vasculitis, Pauci-Immune or ANCA-Associated Vasculitides or ANCA Associated Vasculitides or ANCA-Associated Vasculitide or Vasculitide, ANCA-Associated or Vasculitides, ANCA-Associated and "randomized controlled trial". With the above retrieval methods, a total of 202 literatures were included, as shown in the Figure 1.

Five articles were evaluated by the Cochrane risk offset tool and Revman5.4 as shown in the Figure 2.

We can conclude from the above two pictures that according to the six criteria in the Cochrane Risk Assessment table, four of the five articles score 4 points, indicating a high quality of the articles.

Inclusion criteria

- The diagnosis is consistent with ANCA vasculitis.
- Patients using rituximab or cyclophosphamide/ azathioprine.
- It must be taken regularly for more than one year.
- Or you can have a kidney biopsy that proves vasculitis.

Exclusion criteria

- The follow-up time was less than 1-year.
- Treatment with other immunosuppressant drugs.
- Age younger than 18 years, pregnant women excluded.
- Patients with malignant tumors.

Date extraction

Relevant data are extracted from the article, mainly in the following aspects: name, year, country, observation group/control group, number of observation group/number of control group, complete remission 6, complete remission 12, and complete remission 18, as shown in the following Table 1 and 2.

Table 1:

Name	Year	Country	Experimental/ Control	Number
1. Duvuru Geetha	2014	American	R/C	51/51
2. E. Miloslavsky	2013	American	R/C	99/98
3. Rachel B. Jones	2010	United kingdom	R/C	33/eleven
4. Ulrich Specks	2013	American	R/C	99/98
5. John H. Stone	2021	Boston	R/C	99/98

Table 2:

Complete Remission 6	Complete Remission 12	Complete Remission 18	Quality
31/32	38/39	38/39	4
85/85	no	no	3
25/9	25/9	25/9	4
63/52	47/38	39/32	4
84/81	no	no	4

Statistical analysis

We used Revman5.4 for data analysis, where I2 test and P value are applied to evaluate the statistic heterogeneity [13]. Heterogeneity values of 25, 50 and 75% are designated as low, moderate and high. If heterogeneity exists, random effect model is used to assess the pooled rate and 95% confidence interval, and if not, they would be assessed by fixed effect model [14,15]. The source of heterogeneity is detected by Subgroup analysis and Sensitivity analysis. Sensitivity analysis is to confirm whether any single study influences the overall results, and further confirm the stability and liability of the meta-analysis. The presence of publication bias is evaluated by funnel plots. The analysis is mainly based on the following indicators.

After screening, a total of 5 literatures were included, which were divided into observation group (Rituximab) and control group (Cyclophosphamide). The same indicators were extracted from the articles for data analysis, as shown in the figures.

Complete response at 6 months, 12 months, and 18 months were compared (Figure 3).

Judging from the above three pictures, we can conclude that the effect of rituximab on complete response rate is more obvious than that of cyclophosphamide, and the results are as follows: (6 complete remission Chi^2=0.46 df=1 I^2=0%, 12 complete remission Chi^2=0.31

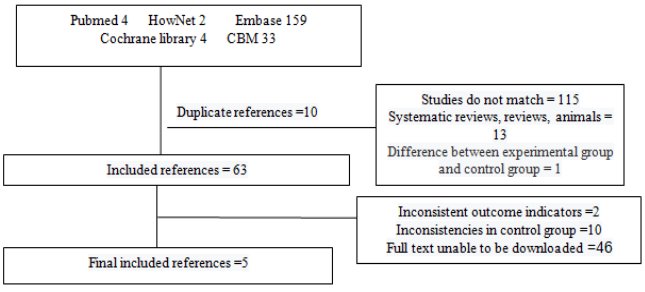

Figure 1: Retrieval methods for total 202 literatures.

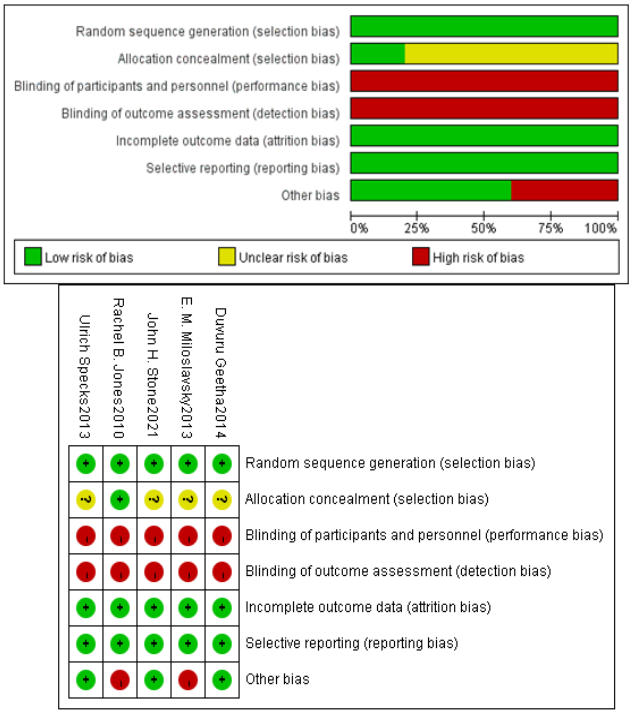

Figure 2: Cochrane risk offset tool and Revman 5.4.

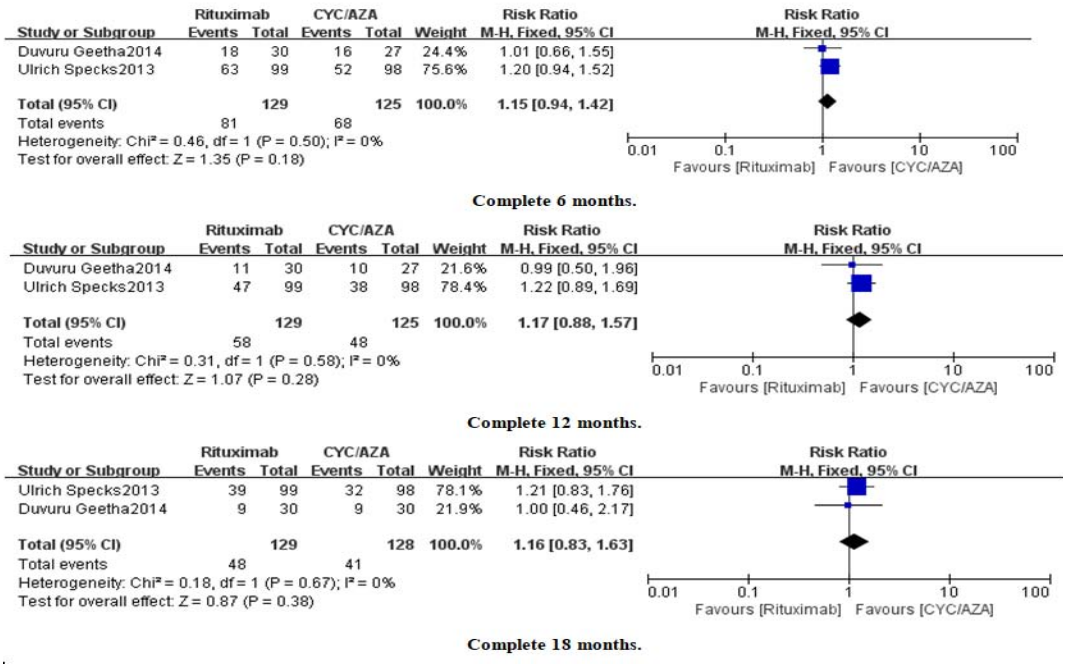

Figure 3: Complete response at 6 months, 12 months and 18 months were compared.

df=1 I^2=0%, 18 complete remission Chi^2=0.31 df=1 I^2=0%). The results show no heterogeneity and are statistically significant.

Recurrence remission rates at 6 months, 12 months and 18 months were compared (Figure 4).

According to the above data, the recurrence remission rate of rituximab is lower than that of cyclophosphamide at 6 months, 12 months and 18 months, respectively being (6 remission recurrence Chi^2=0.22 df=1 I^2=0%, 12 remission recurrence Chi^2=0.04 df=2 I^2=0%, 18 remission recurrence Chi^2=0.13 df=1 I^2=0%). The above conditions are met (I^2≥50% P< 0.1).

The results show no heterogeneity, and are statistically significant.

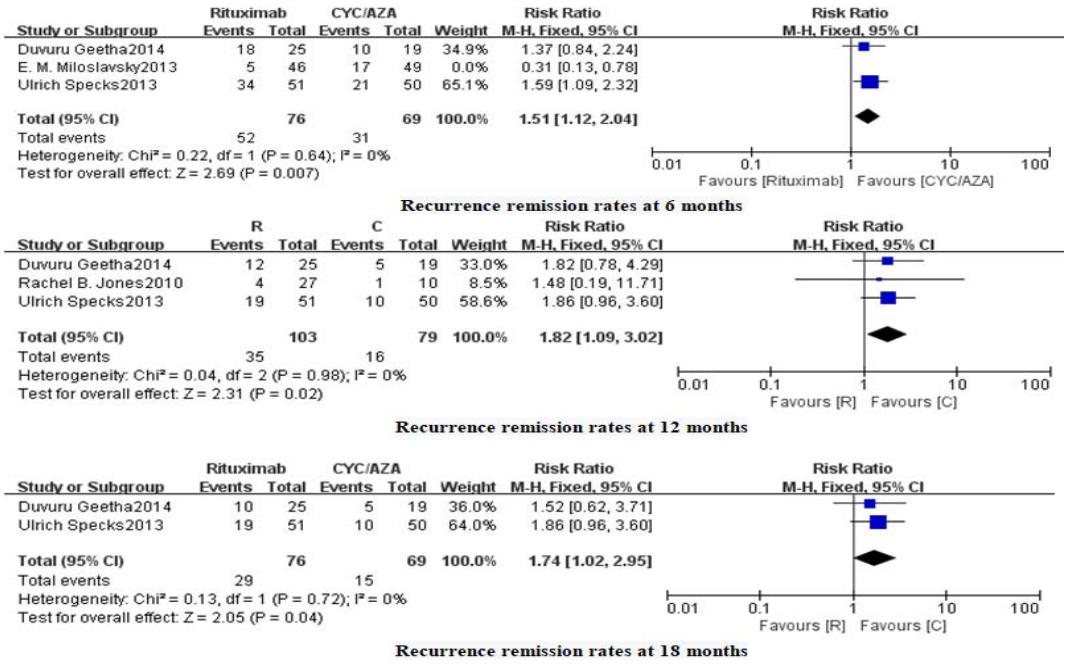

Figure 4: Recurrence remission rates at 6 months, 12 months and 18 months were compared.

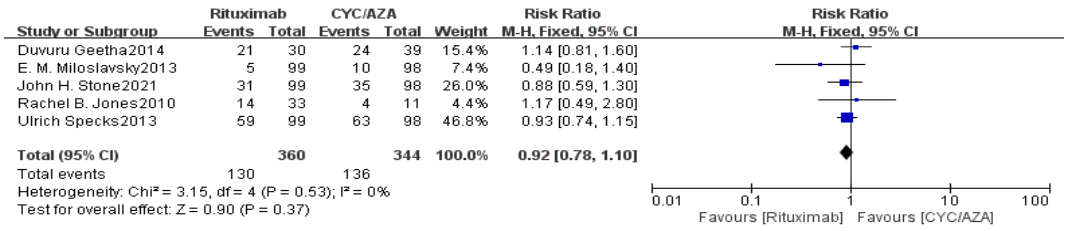

Figure 5:

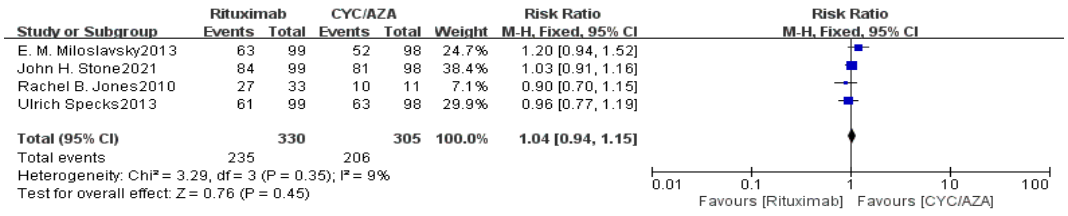

Figure 6: Rituximab and cyclophosphamide reaching primary endpoint were compared.

Adverse event

See Figure 5.

According to the data extracted, rituximab produces less side effect than cyclophosphamide (Chi^2=3.15 df=4 I^2=0%), which is statistically significant.

Rituximab and cyclophosphamide reaching primary endpoint was compared (Figure 6).

It can be seen from the figure that rituximab achieves clinical cure earlier than cyclophosphamide, which is statistically significant (Chi^2=3.29 df=3 I^2=9%).

Rituximab and cyclophosphamide failing to reach primary endpoint were compared (Figure 7).

According to the above data, there exists statistical significance between the two (Chi^2=1.72 df=2 I^2=0%).

Rituximab and cyclophosphamide of Grade 3 and higher were compared (Figure 8).

Compare ANCA with various types of complete remission at 6 months (Figure 9).

The above figure shows that rituximab also has a good effect on different types of ANCA vasculitis, which is statistically significant

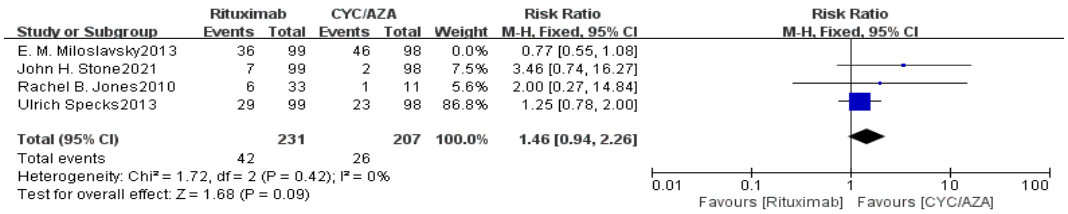

Figure 7: Rituximab and cyclophosphamide failing to reach primary endpoint were compared.

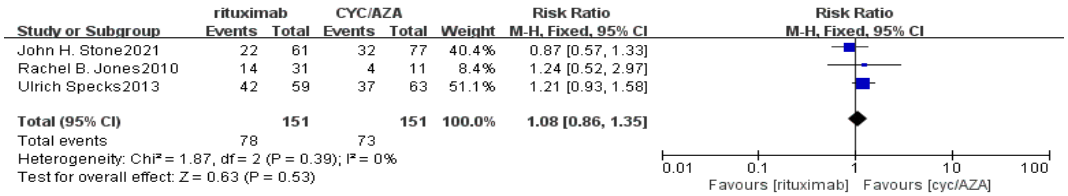

Figure 8: Rituximab and cyclophosphamide of Grade 3 and higher were compared.

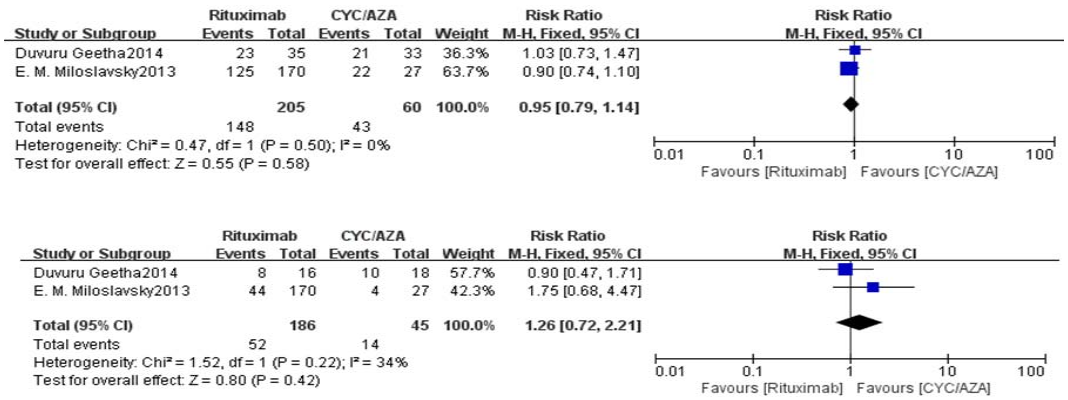

Figure 9: Compare ANCA with various types of complete remission at 6 months.

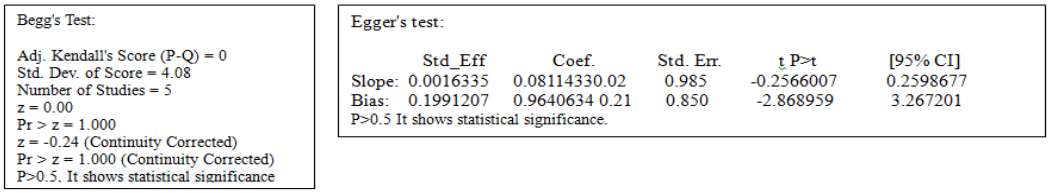

Figure 10: Calculate publication bias.

(Chi²=1.52 df=1 I²=34%).

Publicans bias

Stata is used to calculate publication bias, as shown in the following Figure 10 and 11.

The above figure shows that there exists no significant evidence of publication bias for the remission rates with rituximab in AAV patients when the funnel plot is analyzed.

Discussion

A total of 5 articles were included after screening, all of which were followed the randomized controlled experiment and divided into the observation group and the control group (Rituximab/CYC). We extracted the same data from the 5 articles for comparison of effects of the observation group and the control group on ANCA remission respectively. Immunosuppressants are first-line drugs for the treatment of ANCA, but due to their obvious side effects, patients cannot achieve clinical cure. Therefore, a new drug with the same effect as immunosuppressants and less adverse effect or even better than immunosuppressants is explored.

In the past, advances have been made in the treatment of AAV, GPA and MPA no longer kill patients within days or weeks, and long-term cyclophosphamide treatment has been replaced by short-term low-dose cyclophosphamide treatment, followed by "step-down"

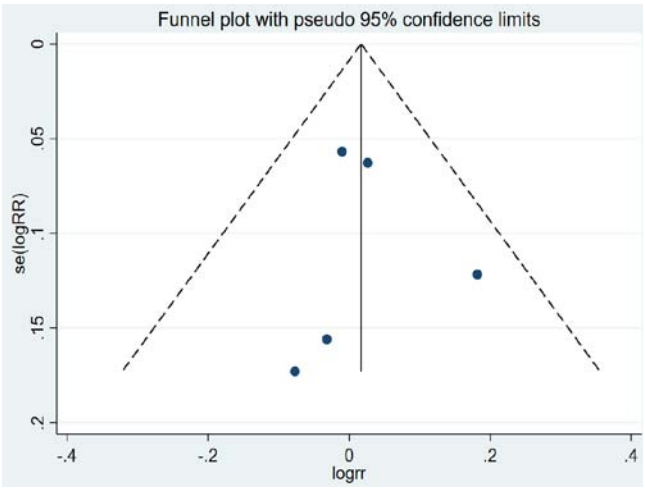

Figure 11: Complete remission.

to AZA or other agents. However, this treatment regimen does not reduce drug toxicity and disease recurrence.

The following conclusions can be drawn from the published articles: First, rituximab and cyclophosphamide are equally effective in inducing remission in ANCA vasculitis with renal damage. Second, the recurrence rate of ANCA vessels is relatively high in the 6-month period. The disease can be controlled with the current regimen, but the disease can easily occur to pr3-ANCA positive patients, if ANCA titer elevated and B cells detected. Third, rituximab and cyclophosphamide have the same effect on severe ANCA vasculitis in inducing remission. Fourth, in patients with severe ANCA vasculitis, a single dose of rituximab has the same the effect with continuous application of immunosuppressants in inducing remission. Fifth, rituximab is not lower than cyclophosphamide in ANCA.

Treatment

Cyclophosphamide is a recommended component of induction therapy for ANCA-associated vasculitis, but can cause many adverse reactions, such as infection, cancer, infertility. To reduce the adverse reactions of cyclophosphamide, we must choose an appropriate treatment plan. The use of rituximab offers the opportunity to further reduce exposure to cyclophosphamide. Rituximab is not associated with the significant increase in infectious complications when used in combination with methotrexate for treatment of rheumatoid arthritis [16] or with chemotherapy for treatment of non-Hodgkin's lymphoma [17]. Furthermore, the use of rituximab, unlike cyclophosphamide, rarely results in profound leukopenia

ANCA vasculitis is prone to recurrence, which is still a challenge for us. It has been shown in a literature that patients with granulomatosis with polyangiitis, proteinase 3-ANCA positivity, and relapsing disease at baseline are at the highest risk for relapse.

Rituximab exerts its effect predominantly through B-cell depletion. Part of cyclophosphamide's therapeutic effect may be mediated with control on B-cell autoreactivity through B-cell suppression [18]. B-cell-derived ANCA is implicated in the pathogenesis of vasculitis, and ANCA negativity after induction therapy is associated with a reduced risk of relapse [19]. Rituximab effectively induces B-cell depletion in all patients, but nearly all the patients show reconstitution of peripheral-blood B cells in 18 months. Previous studies have characterized the effects of cyclophosphamide on the numbers and functions of B cells in blood [20-27].

We have searched the relevant literatures from a Chinese database and several English databases. Analysis on these literatures shows the following results. For complete response, on the one hand, we made comparison among the three periods of 6 months, 12 months and 18 months of relief, and concluded that rituximab, compared with cyclophosphamide, can maintain longer complete remission. However, we were kind of limited in literature reference, and it is expected to include more data in the future meta-analysis, so as to better illustrate the effect of rituximab. Rachel B. Jones has reported that rituximab-based regimen is not superior to the conventional cyclophosphamide regimen. Both treatment groups have high rates of sustained remission and severe adverse effects, which is consistent with previous reports. For remission of relapse, we analyzed and evaluated the remission of relapse at 6, 12 and 18 months respectively from the included literature. Although the included literature data are limited at scale, we can still conclude that rituximab can maintain remission for a long time, but at a low recurrence rate. Disease recurrence in ANCA vasculitis remains a challenge. One of the literatures reports that high-risk patients frequently have relapse after remission induced by cyclophosphamide and maintained with azathioprine therapy. When remission is induced with rituximab, recurrence probability can be increased by B cell redetection. Retreatment with rituximab has recently been shown to maintain complete remission in patients who are positive for proteinase 3-ANCA and who have had relapsing disease [28,29]. This shall be taken into consideration. The idea that conventional remission or repeated consumption of B cells is more effective in treating the disease after initial rituximab induced remission remains to be further investigated. ANCA titer and B cell measurements are often used to predict disease recurrence, but neither reflects disease recurrence. In terms of adverse reactions, we can see from the figures that there exist certain differences between rituximab and cyclophosphamide, which is inconsistent with one of the literatures. Actually, however, there are differences in classification of adverse reactions. For example, in comparing the safety of the two, we analyzed the adverse events in patients while they were receiving their originally assigned treatment. There were fewer episodes of leukopenia of grade 2 or higher (a white-cell count of <3000 per cubic millimeter) in the rituximab group than in the cyclophosphamide-azathioprine group (5 *vs.* 23, P<0.001). There was no significant difference between the treatment groups in the number or rate of infections of grade 3 or higher.

This paper has the following shortcomings: a) In the process of searching for suitable literatures to be included in the study, some of original literatures cannot be downloaded or data in them are incomplete, which leads to a small number of included literatures and cannot be used, free of worry. b) Through quality evaluation, we set scores for the included literature in quality evaluation, and the quality of the literatures was not particularly high. c) All of the patients with ANCA vasculitis included in our study have organ damage, while those without organ injury cannot be included, resulting in incomplete data and lack of corresponding comparison between the two. d) With regard to analysis on certain subgroup, data size is

relatively small for certain comparisons.

Advantages of this paper are as follows: a) Randomized controlled trials are used in all the literature we included, following rituximab in the observation group and cyclophosphamide in the control group. b) There are few meta-analyses of rituximab versus cyclophosphamide in ANVA vasculitis. c) This study is prospective and provides a basis for future treatment of ANCA vasculitis.

There has been a literature report on the induction of remission of ANCA vasculitis through comparison between mycophenolate and cyclophosphamide, and the conclusion is that mycophenolate has the same therapeutic effect as cyclophosphamide, which, however, shall be supported by further studies.

In brief, complete remission of rituximab is higher than that of cyclophosphamide in induction of easing with cyclophosphamide, rituximab in 6 months, 12 months and 18 months. Besides it can reduce adverse reactions, and requires a longer time. Rituximab may replace cyclophosphamide in clinical to become a first-line drug, which however, requires a higher size of data for verification due to the smaller amount of data included in this research.

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