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Rituximab versus cyclophosphamide in the management of Wegener's granulomatosis: A systematic review and meta-analysis

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Abstract
Background: Wegener granulomatosis is an auto- immune disease that causes damage in blood vessels, type of Antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis. The treatment by Rituximab versus Cyclophosphamide that different mechanism on CD20 on B cell and alkylating DNA due to replication dividing cells like neutrophils and lymphocytes.
Methods: We systematically searched electronic databases, including PubMed, Scopus, Elsevier and Cochrane journals, spanning from each database's inception to Aug 10, 2024.Following guidelines specifiedin the Preferred Reporting Items for Systematic Reviewsand Meta-Analyses (PRISMA), Pooled effect estimates with 95% confidence intervals will be calculated using random-effects model.
Results: Four studies have included in this meta- analysis total 504 patients after events that are evaluatingthe safety and effectiveness of Rituximab compared to Cyclophosphamide in patients with Antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis and two studies focusing on patient with renal diseases.
Conclusion: This meta-analysis indicates that Rituximab has a higher mortality rate. On the other hand, Cyclophosphamide shows a higher vasculitis damage score. By Birmingham Vasculitis Activity Score for Wegener's Granulomatosis there is no significant preference between the two drugs. It is recommended for patients with ANCA to use a different investigation to confirm from a positive result to balance efficacy and minimize harmful consequences.

Keywords : Cyclophosphamide, Rituximab, wegener's granulomatosis, autoimmune disease

Introduction
Antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis is a disease that can be due to damage tovarious organs in patients and life-threatening complications. Wegener's granulomatosis is an autoimmune disorder that due to vasculitis (inflammation of blood vessels) leads to damage in tissue in various organs and has symptoms (ex: SOB, joint pain, skin rashes, nosebleed).
We can decrease of side effect and complication by Twoprimary treatments for this condition are Rituximab and Cyclophosphamide. Rituximab, a monoclonal antibody medication used to treat autoimmune diseases and some types of cancer, has shown promising results in inducing remission, particularly in patients with relapsing diseases. Also. It can work on CD20 protein on surface on B cells. On the other hand, Cyclophosphamide is cytotoxic drug, a potent immunosuppressive drug, has long been used to treat autoimmune diseases such as Antineutrophil cytoplasmic antibody (ANCA)-associatedvasculitis, it worked by alkylating DNA due to replication dividing cells (like neutrophils and lymphocytes).

Methods
Search strategy Following guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we systematically searched electronic databases, including PubMed, Scopus, Cochrane, Elsevier journals, spanning from each database's inception to August 8, 2024.

Our search strategy involved a combination of relevant keywords and standardized index terms tailored to the comparison between effectiveness Rituximab and Cyclophosphamidein patients with Antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis.

Selection Criteria

Type of studies

This review and meta-analysis will look at studies that watched patients over time or looked back at records. These studies need to have included ten or more people with Antineutrophil cytoplasmic antibody (ANCA). The research must compare what happened to patients who took Rituximab versus those who took Cyclophosphamide. All patients in the studies should have Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Types of intervention

The focus of our study is the use of a placebo in patients with a condition called Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. We are looking at how Rituximab and Cyclophosphamide work in patients with a specific type of condition known as Wegener granulomatosis. Like a study by Geetha D in 2014 [3], we have divided patients into two groups, each receiving a different drug along with a placebo.

Types of outcomes measures

Eligible studies must focus on clinically relevant outcomes regarding the efficacy and safety of rituximab and cyclophosphamide. These results can include complications such as infections, leukopenia and hypersensitivity reactions.

Exclusion criteria

Studies will exclude if they do not involve human subjects; are not publishing in English; have a sample size smaller than ten in either Rituximab and Cyclophosphamide; present overlapping data from the same institution(s); or have a median follow-up duration of less than 6 months. Studies with inadequate reporting of outcomes, such as failing to specify the exact number of events and the total patient-years for comparisons between the Drugs approaches, will be excluding. Furthermore, studies that do not report outcomes specifically for the effect Rituximab and cyclophosphamide will be excluded. Reviews, case reports, conference abstracts, letters to the editor, and editorials will also be excluding.

Quality assessment

Before conducting the statistical analysis, we assessed the risk of bias and the quality of the included studies. For the two eligible RCTs, we used the revised RoB-2 Cochrane tool and conducted the assessment using Cochrane Review Manager Web.

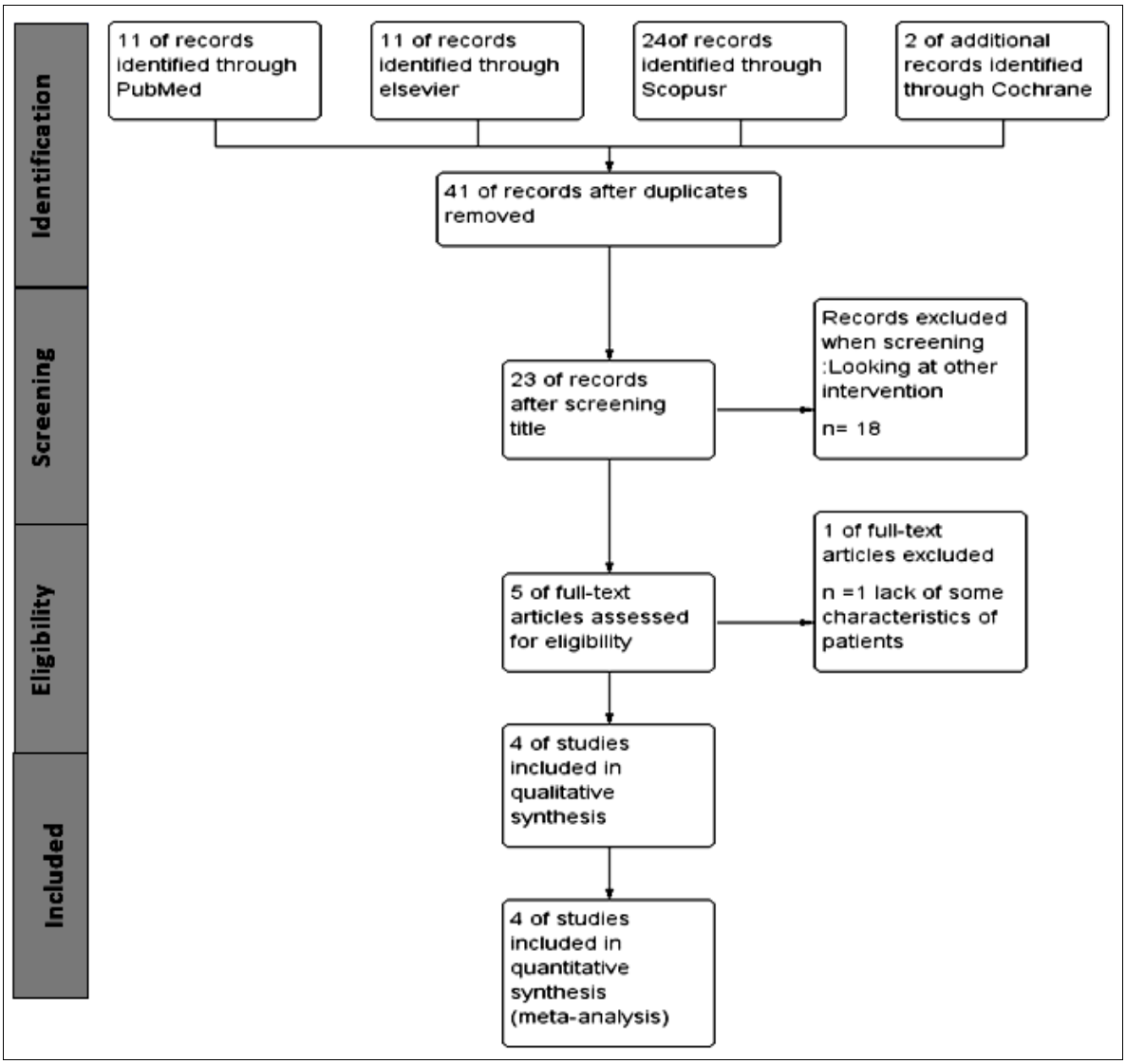

Fig 1: The flow sheet of search results according to PRISMA guidelines

THE PRISMA flowchart provides a detailed description of the selection process for the systematic review and meta-analysis on the use of Rituximab and Cyclophosphamide in Patient with antineutrophil cytoplasmic antibodies (ANCA) associated with vasculitis. Initial research generated a total of forty-eight records from different databases: 11records from PubMed, twenty-four records from Scopus, two records of Cochrane and eleven additional records identified from Elsevier. After removing duplicates, forty-one records remained for further evaluation. The selection process started with these forty-one records, of which eighteen were excluding to focus on other interventions or to be irrelevant to the research question. This exception left twenty-three records for title projection, after that, there were other files they are excluding due to lack of characteristics and had no results. Five full-text articles were evaluated for their eligibility, and four studies met the inclusion criteria. THIS4 studies were later included in the systematic review and quantitative synthesis (meta-analysis).

Table 1: Summary of the four studies compared (Rituximab vs Cyclophosphamide)

Study	Sample Size	Study Design	Population	Data Collection	Outcome
Stone JH et al. (USA and Netherlands, 2010) [6]	197	Randomized Controlled Trial (RCT)	Patients with severe antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis	Rituximab (375 mg per square meter of body surface area per week for 4 weeks) compared to cyclophosphamide (2 mg per kilogram of body weight per day)	Treatment with rituximab was not inferior to daily treatment with cyclophosphamide for inducing remission. The induction of remission in severe vasculitis is associated with ANCA and may be superior in recurrent diseases. No significant difference in relapse rates between groups.
Jones RB et al. (Multiple centers of Europe, 2014) [4]	44 Patients	Randomized Controlled trial (RCT)	Patient with renal problem and severe antineutrophil cytoplasmic antibody (ANCA)	Rituximab compared to Cyclophosphamide	At 24 months, the result rates are compounded death, terminal renal failure and relapse did not differ between groups. Rituximab group, the return of B lymphocytes was regarding the return.
Geetha D et al. (North America, Europe, and Asia, 2014) [3]	102	Randomized Controlled Trial (RCT)	Patients with renal disease and severe antineutrophil cytoplasmic antibody (ANCA)	Rituximab follow-up compared to placebo	Primary endpoint: full remission. Secondary endpoints: remission at 12 and 18 months, slope of growth in 18-month eGFR, rates of disease recurrence, and serious adverse events.
Miloslavsky EM et al. (USA,Europe, 2013) [5]	170 Patients from 197	Randomized controlled trial (RCT)	Patient with Severe Antineutrophil Cytoplasmic Antibody–Associated Vasculitis	Rituximab compared to Cyclophosphamide and azathioprine	Current treatment regimens are effective in controlling AAV, but in about a quarter of patients, active disease persists or recurs within the first six months despite treatment. PR3-ANCA positivity is a risk factor for serious disease recurrence or progression. ANCA titers and B-cell detectability are. poor predictors of disease relapse and remission during the first six months.

The (Table 1) presents data from four randomized controlled trial conduct in different countries, focusing on the patients with severe Antineutrophilcytoplasmic antibody (ANCA) associated with vasculitis. Additions, two studies were focusing on patients with renal diseases Jones RB *et al.* (2014) [4] and Geetha D *et al.* (2014) [3]. The study by Stone JH *et al.* (2010) [6] involved 197 patients divided two groups (99 patients taken Rituximab (375 mg per square meter of body area per 4 weeks) vs 98 patients taken Cyclophosphamide (2mg per kilogram of body weight per day). The secondary study Jones RB *et al.* (2014) [4] was focusing on patients with renal diseases divided into twogroups (33 Rituximab vs 11 Cyclophosphamide).

This study had nine dead patients ninety-six patient's deaths fromgroup taken Rituximab vs 3 patient's deaths from group taken Cyclophosphamide. Also. The third study found that patients with renal disease were investigating renal (eGFR) at 12, 18 months. This study included patient taken Rituximab before placebo versus patients taken Cyclophosphamide before placebo, azathioprine and show adverse effects for each study. The last study was content 197 patients (3 deaths, twenty-four remissions, 170 completed with research), this study investigated ANCA and clearing risk factors for serious diseases.

(Table 2) compare Patient characteristics from four studies. Stone JH 2010 [6] study included 99 patients in the Rituximab group (male 46 patients + female 54 patients), 98patients in the cyclophosphamide group (male 54 patients + female 46 patients). Geetha D 2014 [3] consisted of patients receiving rituximab (males forty-seven, females fifty-three vs. males fifty-seven, females43 in the cyclophosphamide group) and this study had a BVS/WG (Birmingham Wegener's vasculitis activity score granulomatosis). The age group was in both studies by Stone JH 2010 [6] 51.5±14.1 in the cyclophosphamide group, 54.0±16.8. Number footnotes separately in superscripts. Place the actual footnote at the bottom of the column in which it was cited. Do not put in Rituximab group and Geetha D 2014 [3] study wasaging of patent fifty-four in Cyclophosphamide group, fifty-sixin Rituximab group. Antineutrophil cytoplasmic antibody (ANCA) was the most thing in Stone JH 2010 [6] (98% in Rituximab group vs 96% in Cyclophosphamide. We can determine type of ANCA by enzyme-linked immunosorbent assay (ELISA), the types of ANCA are (PR3 (proteinase 3), MPO (myeloperoxidase)) , 3 studies from 4 studies show are in patient taken Rituximab have percent of ANCA more than patient taken Cyclophosphamide

Table 2: Patients characteristics

Group	Age cyclophosphamide	Age Rituximab	Gender Ritusimab	Gender Cyclophosphamide	BVAS/WG Ritusimab	BVAS/WG Cyclophosphamide	ANCA(%) Rituximab	ANCA (%) Cyclophosphomide
Stone JH 2010	51.5+14.1	54.0+16.8	Male 46 Female 54	Male 54 female 46	8.5+3.2	8.2+3.2	98%	96%
Jones RB 2014	NA	NA	33	11	NA	NA	63%	54%
Geetha D 2014	54	56	Male 47. Female 53	Male 57. Female 43	8.7(2.74)	8.7(3.51)	59%	55%
Miloslavsky EM,2013	NA	NA	99	98	8(1.6)	8(1.4)	86%	86%

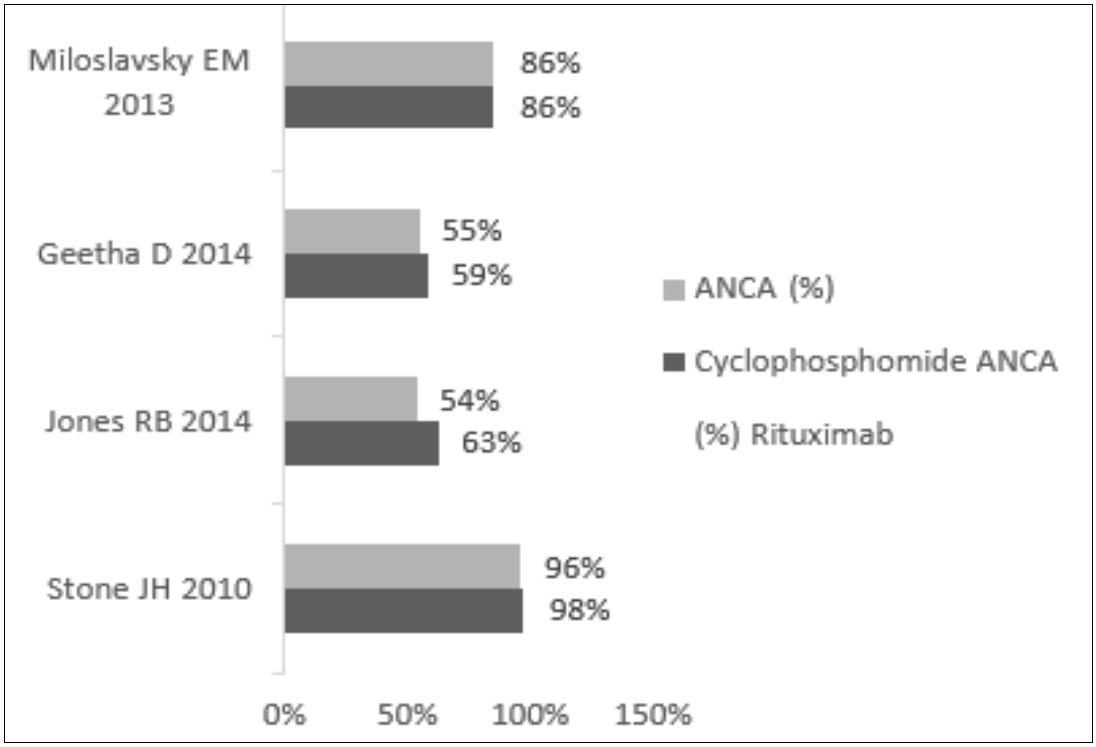

Fig 2: Percent of Antineutrophil cytoplasmic antibody (ANCA) in patients in studies

This image is show percents of Antineutrophil cytoplasmic antibody (ANCA) for each study and for two drugs, Antineutrophil cytoplasmic antibody (ANCA) is different from studyto other. Stone JH 2010 [6] has (98% in Rituximab groupvs 96% in Cyclophosphamide) and it more than other studies while Geetha D 2014 [3] study has lower ANCA in the studies (Rituximab 59% vs Cyclophosphamide 55%) in the Miloslav Sky EM 2013 has equal percent for two drugs that 86% 3 studies from 4 studies show are in patient taken Rituximab have percent of ANCA more than patients taking Cyclophosphamid.

The risk of bias assessment for the systematic review and meta-analysis on the use of the Rituximab compared to Cyclophosphamide in patients with antineutrophil cytoplasmic antibody (ANCA) associated with Vasculitis includes evaluations of four studies: Stone JH 2010 [6], Jones RB 2014 [4], Geetha D 2014 [3], Miloslavsky EM 2013 [5]. The assessment indicates that all studies have a minimal risk of bias in most categories, such as selection, performance, detection, attrition, and reporting biases. Key areas like random sequence generation, allocation concealment, blinding, and data reporting consistently rated as insignificant risk, reflecting robust methodologies.

This consistent rating of minimal risk across these key domains suggests that the individual studies conducted with robust methodologies, minimizing the potential for biased outcomes. In the overall assessment across the studies, more of the categories continue to reflect an insignificant risk of bias. Random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases were all reported with 100% minimal risk.

However, the concerns were noting in the categories of performance bias and detection bias, where approximately 33% of the assessments indicated an unclear risk of bias. This ambiguity arises from the blinding of participants and personnel and the blinding of outcome assessment, which are crucial for preventing performance and detection biases.

Overall, the studies demonstrate a strong methodological quality with minimal risk of bias, lending credibility to the findings of the systematic review and metanalysis. Despite the minor concerns in performance and detection biases, the predominance of low-risk ratings supports the validity and reliability of the conclusions drawn regarding the effectiveness of the Rituximab compared Cyclophosphamide in patient with antineutrophil cytoplasmic antibody (ANCA) associated with Vasculitis.

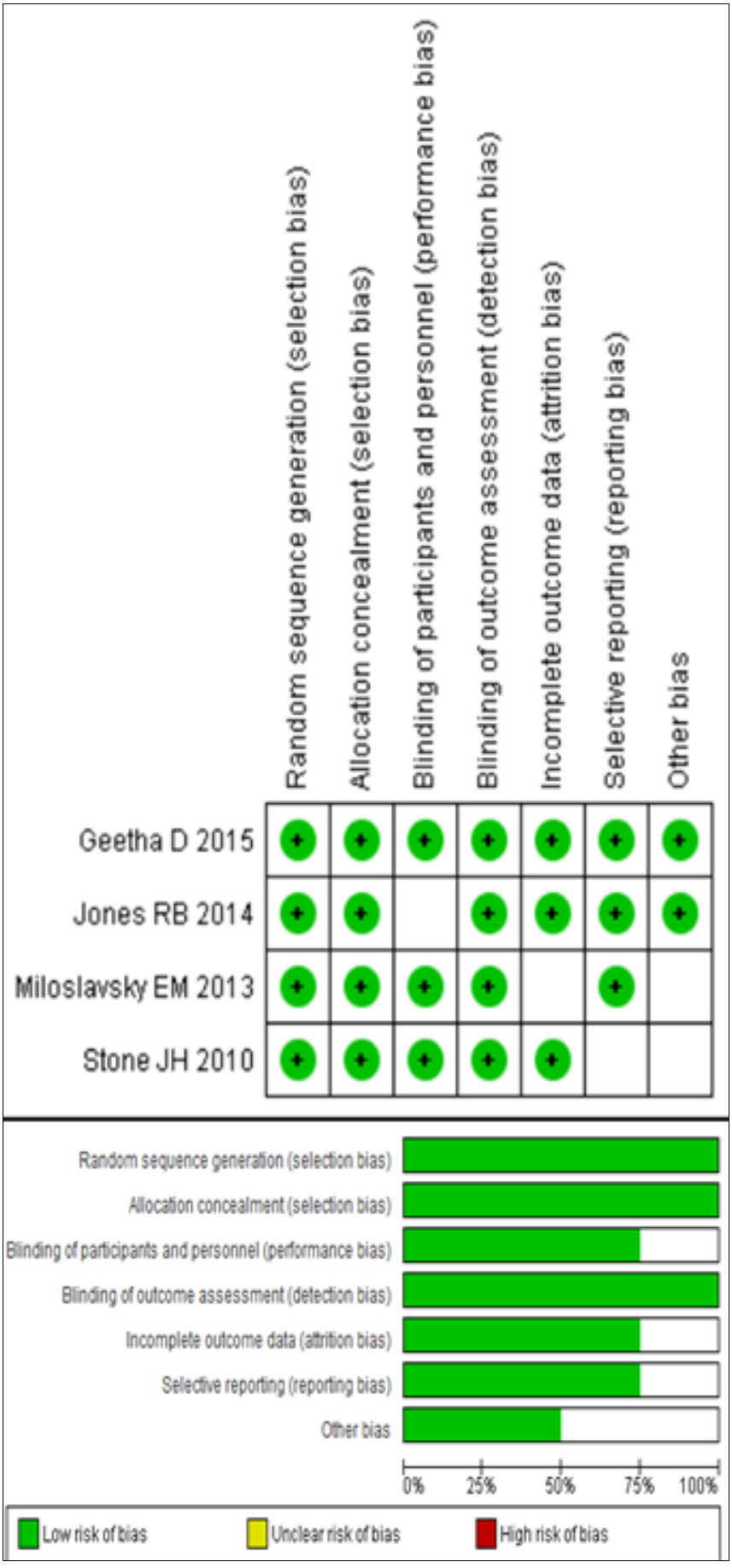

Fig 3: Risk of Bias Assessment using RoB-2 tool

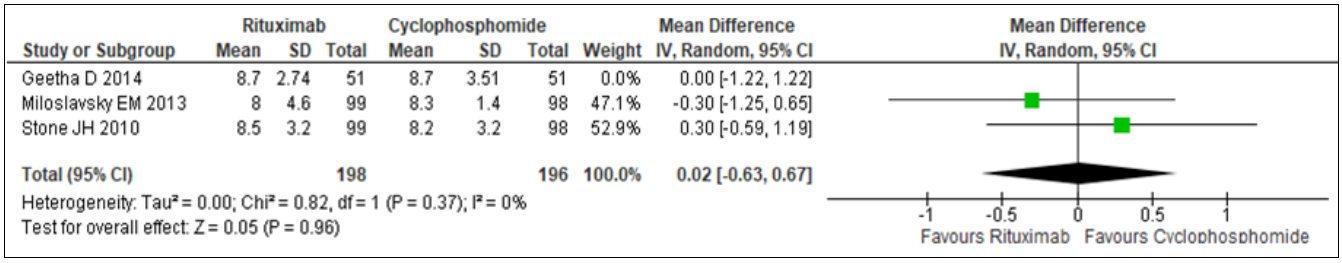

Fig 4: The forest plot of the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis of the three included studies using a random effect model

This image is a forest plot from a meta-analysis comparing effectiveness between two drugs Rituximab vs Cyclophosphamide) in patient with antineutrophil cytoplasmic antibody (ANCA) associated with Vasculitis: It includes data from three studies", Stone JH 2010 [6], Geetha D 2014 [3], Miloslavsky EM 2013 [5]". For each study, the mean, standard deviation (SD), and total number of participants in both Rituximab and cyclophosphamide groups are listed. The mean difference between these groups, along with the 95% confidence interval (CI), is provided for each study. The inverse variance method (IV) and a Random-effect model (Random) were used to calculate these differences. The weight assigned to each study in the meta-analysis is based on the samplesize and variance whether the differences in results across studies are due tochance, with a p-value of 0.96 and I^2 of 0% indicating no heterogeneity. The make sure that the overall evidence was not dependent on single studies we conducted a sensitivity analysis in multiple scenarios excluding a study in each scenario to make sure the effect size was not dependent on any individual event studies. The overall mean difference between the Rituximab and the cyclophosphamide don't favor (pooled effect size 0.02 ,95%Cl [-0.63to 0,67], P=0.96. Pooled studies were not homogenous (chi0.82, P=0.37, I=0%).

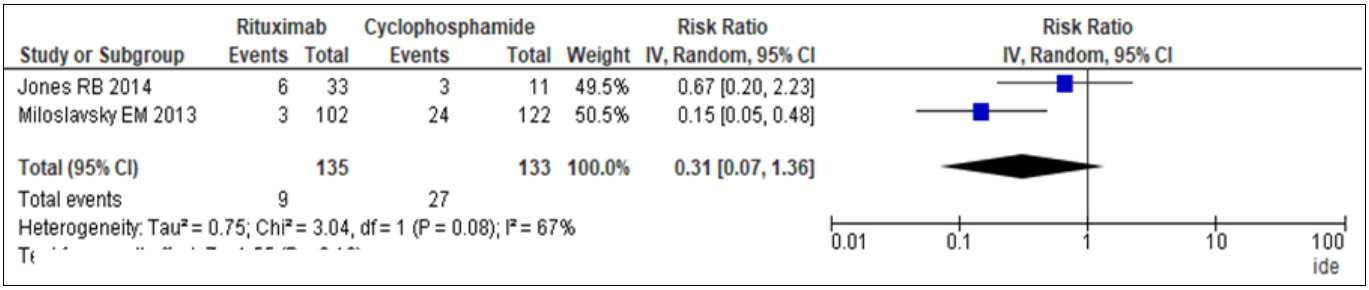

Fig 5: The forest plot of Uncontrollable and deaths patients in the 2 included studies using a random-effects model

This image is a forest plot of a meta-analysis comparing uncontrolled and each drug because of the higher risk between the two drugs. (Rituximab vs Cyclophosphamide) in a patient with antineutrophil cytoplasmic antibodies (ANCA) associated with vasculitis: include data from two studies, "Jones RB 2014 [4], Miloslavsky EM 2013 [5]". For each study, the events (death or uncontrollable) and the total number of Participants in the Rituximab and Cyclophosphamide groups are listed.

The hazard ratio between these groups, as well as the 95% confidence interval (CI), is provided for each study. The inverse variance method (IV) and the random effects model (Random) were used.to account for these differences. The weight assigned to each study in the meta-analysis is based on sample size and variance. U the Chi-square test for heterogeneity assesses whether differences in results between studies are due to chance, with a p-value of0.12 and an I^2 of 67% indicating a lack of heterogeneity. The overall risk ratio between rituximab and cyclophosphamide is favorable rituximab (RR 0.31 95% CI [0.07 to 1.36], P = 0.07).P=0.12). Pooled studies were homogeneous (chi=3.04, P=0.08, I=67%).

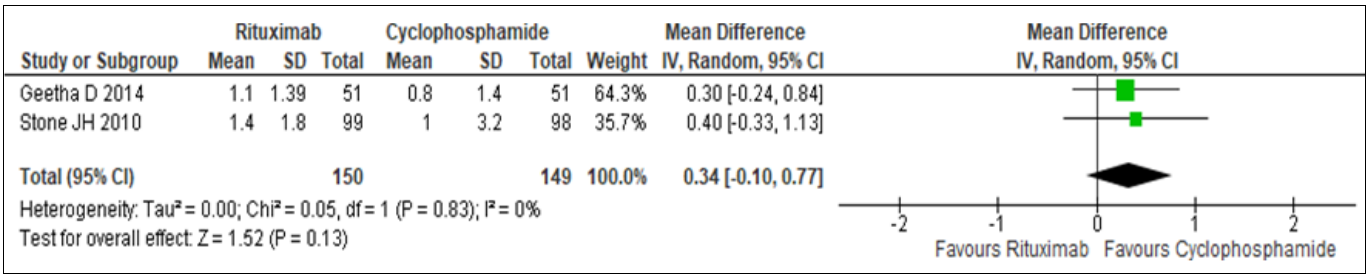

Fig 6: The forest plot of the Vasculitis Damage Index of the 2 included studies using a random-effects model

This image is a forest plot from a meta-analysis comparing effectiveness in Vasculitis Damage Index between two drugs (Rituximab vs Cyclophosphamide) in patient with antineutrophil cytoplasmic antibody (ANCA) associated with Vasculitis: It includes data from two studies, "Stone JH 2010 [6], Geetha D 2014 [3]". For each study, the mean, standard deviation (SD), and total number of participants in both Rituximab and Cyclophosphamide groups are listed. The mean difference between these groups, along with the 95% confidence interval (CI), is provided for each study. The inverse variance method (IV) and a Random effect model (Random) were used to calculate these differences. The

weight assigned to each study in the meta-analysis is based on the sample size and variance. The Chi-square (Chi^2) test for heterogeneity assesses whether the differences in results across studies are due to chance, with a p-value of 0.13 and I^2 of 0% indicating no heterogeneity. The overall mean difference between the rituximab and the cyclophosphamide favored the cyclophosphamide (pooled effect size 0.34,95%Cl [-0.1 to0.77], P=0.13. Pooled studies were homogenous (chi=0.05, P=0.83, I=0%)

Discussion

Our meta-analysis, we included all studies that compared between two drugs (Rituximab vs Cyclophosphamide) in patients with ANCA associated vasculitis and renal disease. We focus on patient with Wegener granulomatosis, and we evaluated the two drugs by Vasculitis damage index and uncontrollable, deaths. In addition, side effect for each drug. Also, we considered studies that patient remission and relapsed. Our analysis included critical investigations in patients with renal diseases such as ANCA and leukocytes, number B Cell and sensitivity surface for B cell (because given Rituximab is mechanism on B cell surface). Therefore, The Doctors must be careful ensure of investigations before give any drugs forpatient with ANCA -associated vasculitis. Our study found that cyclophosphamide has a more significant effect on blood vessels with vasculitis damage compared to rituximab, as supported by two studies. These studies indicated that cyclophosphamide scores higher on the Vasculitis Damage Index. Conversely, rituximab was associated with a higher risk of uncontrolled disease. Using the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG), two studies reported effect sizes of 0.02, with one favoring cyclophosphamide and the other favoring rituximab. This highlights the complexity of choosing the most appropriate treatment and suggests that the decision should be tailored to individual patient profiles regarding Safety and effectiveness in 2 studies were focused on patient with renal studies, we definitive ANCA. In addition, two types are (PR3 (proteinase 3), MPO (myeloperoxidase), Rituximab has higherANCA in some studies, but it was associated with a risk of mortality with 9 patients reported dead in two studies. On the other hand, Cyclophosphamide was found to be uncontrolled in 24 patients after using it and has side effects (ex: fatigue, SOB).

Conclusion

Our systematic review and meta-analysis found a clinically significant reduction in side effects and efficacy of rituximab use and cyclophosphamide in patients with anti-neutrophil cytoplasmic antibodies (ANCA)associated with vasculitis. These results are particularly important. During the process ANCA- associated vasculitis (AAV) with rituximab and cyclophosphamide, we looked in our meta-analysis for this determine which medication is most effective and safe patients with ANCA and kidney disease. Ours Research has shown that rituximab is associated with higher mortality rates and poorer disease control compared to cyclophosphamide. On the other hand, cyclophosphamide has significant side effects, especially for patients with kidney disease, and cyclophosphamide can lead to more serious vasculitis. So, we will be attention to choosing the right treatment for a patient suffering from kidney disease to balance effectiveness and minimize harmful consequences.

Limitation of study

The heterogeneity of treatment in patients with Wegener granulomatosis included in assorted studies makes it challenging to draw definitive conclusions about the Rituximab and Cyclophosphamide efficacy across the spectrum of these complex cases. Future research focusing on compared by effectiveness between Rituximab and Cyclophosphamide would provide more targeted insights into the benefits and limitations of the drugs in these distinct scenarios. It is important to note that this meta-analysis only included two studies specifically investigating renal diseases end stage renal diseases (ESRD) and serum albumen. This limited sample size restricts the statistical power of the analysis and underscores the urgent need for additional research in this area to confirm these preliminary findings and establish more definitive conclusions.

Ethical approval

This meta-analysis is based on previously published studies, Ethical approval or patient consent is not therefore required.

Conflict of Interest

Not available

Financial Support

Not available

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