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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Rituximab Maintenance Therapy for the Management of Granulomatosis with Polyangiitis or Microscopic Polyangiitis: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Authors: Chuong Ho, Lorna Adcock

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) belong to a group of rare autoimmune diseases called antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, with an estimated annual incidence varying from two to 12 cases per million worldwide, and characterized by inflammatory cell infiltration leading to necrosis of the blood vessels.[1-3] Patients with ANCA-associated vasculitis present with a wide variety of signs and symptoms, ranging from skin rash to fulminant multisystem failure, and carry a 2.7-fold increase in mortality compared with the general population.[4]

Treatment of GPA and MPA includes remission induction and remission maintenance.[5,6] Currently, rituximab, a monoclonal antibody, is one of the therapeutic options approved for the induction phase.[7,8] Recently, a number of non-comparative studies have suggested that rituximab, in combination with low-dose glucocorticoids, can also be of value in maintaining remission,[9-22] in which rituximab can be used as repeated cycles in fixed intervals schedule, or as tailored administration based on ANCA reappearance or titre change (disease flare or relapse).[23] This Rapid Response report aims to review the comparative clinical effectiveness of rituximab versus other drugs used as remission maintenance therapy for GPA or MPA. Cost-effectiveness and evidence-based guidelines regarding the use of rituximab as maintenance therapy for patients with GPA and MPA will also be examined.

Research Question

1. What is the comparative clinical effectiveness of rituximab maintenance therapy versus other remission maintenance therapy or rituximab flare/relapse therapy for the management of GPA or MPA?
2. What is the cost-effectiveness of rituximab maintenance therapy versus other remission maintenance therapy or rituximab flare/relapse therapy for the management of GPA or MPA?
3. What are the evidence based guidelines regarding the use of rituximab maintenance therapy for the management of GPA or MPA?

Key Findings

Findings from two RCTs showed that fixed-schedule rituximab was superior to daily azathioprine in maintaining remission up to 60 months follow-up in patients with ANCA-associated vasculitis. Relapse rates were similar between fixed-schedule maintenance rituximab and individually tailored rituximab at ANCA reappearance or titre change. There was no evidence found on the cost-effectiveness of rituximab, or evidence-based guidelines on the use of rituximab, as remission maintenance therapy for GPA or MPA.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD)

databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2008 and July 3, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of all age with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), who received remission-inducing or a response to induction therapy with a combination of glucocorticoids and cyclophosphamide or rituximab
Intervention	Rituximab given as maintenance therapy
Comparator	Drugs used as remission maintenance therapy for GPA or MPA, in combination with low-dose glucocorticoids Retreatment with rituximab upon disease flare/relapse
Outcomes	Q1: Clinical efficacy/effectiveness (e.g., remission, clinical response, laboratory values, quality-of-life, safety) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Heath technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-RCTs, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2008.

Critical Appraisal of Individual Studies

The included clinical trials were critically appraised using and Downs and Black instrument.[24] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 487 citations were identified in the literature search. Following screening of titles and abstracts, 469 citations were excluded and 18 potentially relevant reports from the

electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 14 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 2.

Study Design

Four publications from two RCTs were included in the review.[25-28] Separate outcomes from the first RCT, MAINRITSAN, were reported in three publications,[25-27] and outcomes from the second RCT, MAINRITSAN 2, were reported in one publication.[28] Both trials were open-label, multi-centre RCTs.

Country of Origin

All four studies were performed in France by the French Vasculitis Study Group.

Patient Population

All four studies included adult patients with newly diagnosed or relapsing GPA or MPA in complete remission after induction therapy. The majority of the population in the trials (ranging from 72% to 76%) had GPA.

Interventions and Comparators

The MAINRITSAN trial compared fixed-schedule rituximab 500mg to daily azathioprine 500mg as maintenance remission therapy,[25-27] and MAINTRITSAN 2 trial compared fixed-schedule rituximab 500 mg maintenance therapy to tailored rituximab 500mg therapy at ANCA reappearance or titre increase (disease flare or relapse).[28] Further details on the interventions and comparators are listed in Appendix 2.

Outcomes

Data from the MAINRITSAN trial on short-term and long-term clinical efficacy (e.g., relapse rates, adverse event rates) of rituximab compared to azathioprine as remission maintenance therapy was evaluated at month 28[25] and month 60[27] after study entry. Health-related quality of life (HRQOL) and disability level outcomes as measured by Health Assessment Questionnaire (HAQ) at month 24 were reported in another publication.[26] The MAINRITSAN 2 trial reported comparative clinical efficacy (relapse rates, number of rituximab infusions) between two rituximab regimens (fixed schedule and tailored schedule).[28]

Summary of Critical Appraisal

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

The included clinical studies[25-28] reported data from RCTs; the hypotheses were clearly described, the method of selection from the source population and representation were described, losses to follow-up were reported, main outcomes, interventions, patient characteristics, and main findings were clearly described, and estimates of random

variability and actual probability values were provided. All trials performed calculations to determine that they were adequately powered to detect a clinically important effect. Assessors, but not patients, were blinded to treatment assignment in all studies, which may have impacted the objectivity of the outcomes assessments. Overall, the included studies had strong internal validity.

Summary of Findings

Details of the findings of the included studies are provided in Appendix 4.

What is the comparative clinical effectiveness of rituximab maintenance therapy for the management of GPA or MPA?

The MAINRITSAN trial compared short and long-term clinical efficacy of fixed-schedule rituximab to daily azathioprine as remission maintenance therapy.[25-27]

More patients with ANCA-associated vasculitis had sustained remission at month 28 with rituximab than with azathioprine (the difference was statistically significant), with similar rates of adverse events (severe infection, cancer) between the two groups.[25] At month 24,[26] both rituximab and azathioprine improved HRQOL as measured by SF-36 scores from baseline; the physical scores did not differ significantly between the two groups, while patients on azathioprine had better mental scores than patients on rituximab. Disability scores as measured by the HAQ showed that changes from baseline were unchanged for the rituximab group but worsened significantly for the azathioprine group. The authors concluded that rituximab performed better than azathioprine in short-term clinical efficacy and disability score for remission maintenance therapy.

At month 60,[27] patients on rituximab had less relapse rates, higher relapse-free survival rates and overall survival rates than patients on azathioprine (all differences were statistically significant). Concomitant glucocorticoids use was similar between the two groups. Adverse events such as severe infection, cardiovascular events were similar between the two groups, with risk of cancer higher in patients on azathioprine. The authors concluded that the rituximab-based maintenance regimen was superior to azathioprine-based regimen in sustaining long-term remission for ANCA-associated vasculitis patients, with better overall survival.

The MAINRITSAN 2 trial compared fixed-schedule rituximab maintenance therapy to individually tailored rituximab at ANCA reappearance or titre increase.[28] At month 28, the difference in relapse rates was not statistically significant between the two regimens. Patients on individually tailored rituximab received fewer rituximab infusions than patients on fixed schedule.

What is the cost-effectiveness of rituximab maintenance therapy versus other remission maintenance therapy or rituximab flare/relapse therapy for the management of GPA or MPA?

There was no evidence found on the cost-effectiveness of rituximab maintenance therapy for GPA or MPA.

What is the evidence based guidelines regarding the use of rituximab maintenance therapy for the management of granulomatosis with polyangiitis or microscopic polyangiitis?

There was no evidence found on evidence-based guidelines regarding the use of rituximab maintenance therapy for GPA or MPA.

Limitations

Evidence on the comparative clinical efficacy of rituximab for GPA and MPA was based on a small number of RCTs (two trials) which were not blinded to the patients; this may have affected the objectivity of the findings, in particular for HRQOL outcomes. The majority of the trials' population were patients with GPA, which limits the generalizability of the findings to all people with ANCA-associated vasculitis. There was no evidence found on the cost-effectiveness of rituximab and guidelines on the use of rituximab for ANCA-associated vasculitis maintenance therapy.

Conclusions and Implications for Decision or Policy Making

Limited evidence from the included studies showed that rituximab was superior to azathioprine in maintaining remission, with similar rates of adverse events, up to 60 months follow-up, in patients with ANCA-associated vasculitis, in particular with GPA, which occupied the majority of the trials' population. Rituximab was superior to azathioprine in reducing global disability as measured by the Health Assessment Questionnaire (HAQ) up to 24 months follow-up. Relapse rates were similar between fixed-schedule rituximab maintenance therapy and individually tailored rituximab at ANCA reappearance or titre change. No cost studies or guidelines on the use of rituximab as remission maintenance therapy for GPA or MPA were found.

Reviews based on non-comparative studies concluded that rituximab for maintenance therapy is still experimental, but the results are hopeful.[29,30] To the best of our knowledge, our review is the first review based on the most updated RCTs on the comparative efficacy of rituximab, with findings suggesting that the use of rituximab for maintenance therapy could be considered. Cost-effectiveness studies are required to understand all the cost associated with rituximab maintenance therapy, and evidence-based guidelines are needed to clarify the roles of rituximab as remission maintenance therapy for GPA or MPA,

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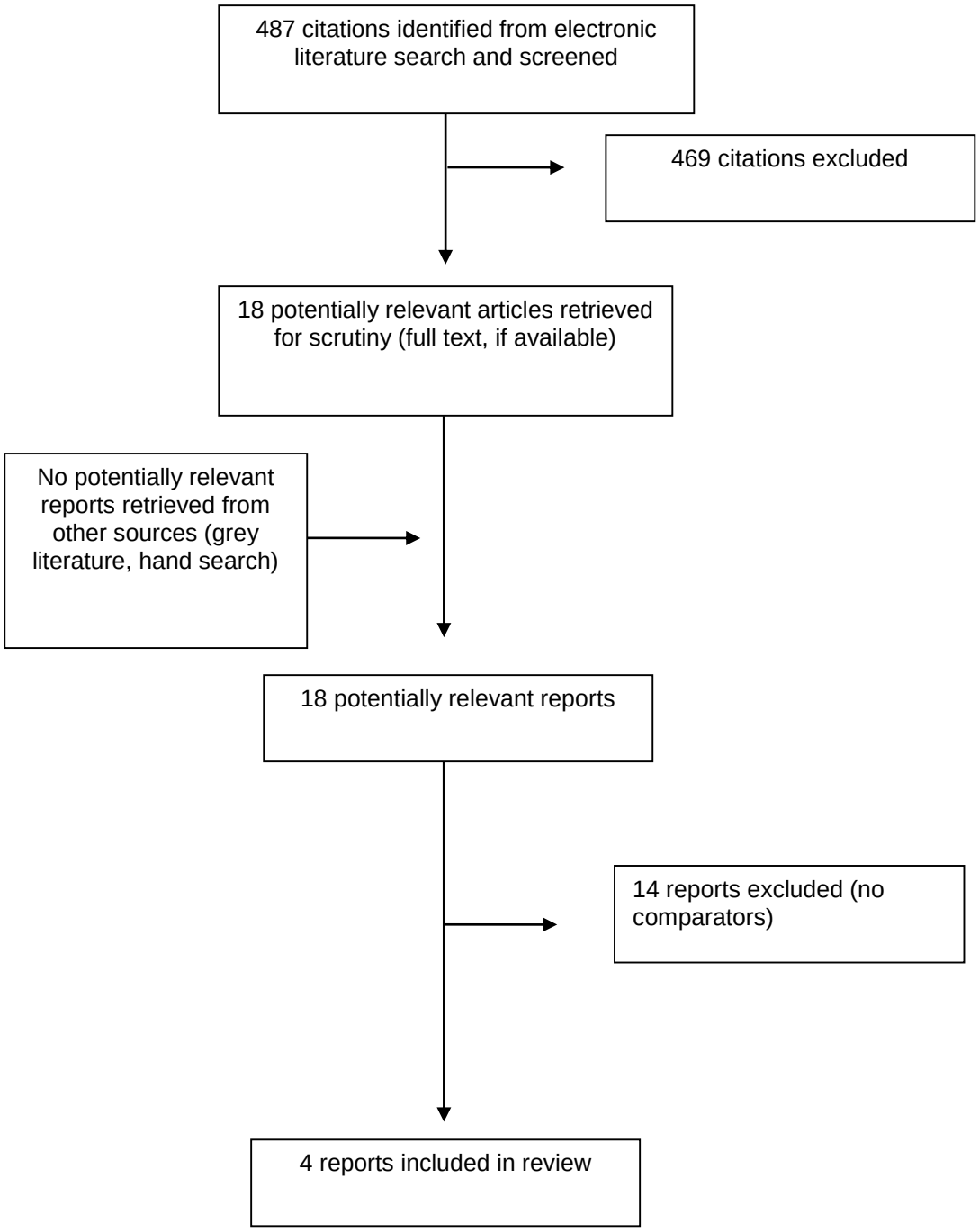
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Clinical Studies

First Author, Year, Country	Study Design Objectives	Intervention Comparators	Patients	Main Study Outcomes
Guillevin,[25] 2014, France (MAINRITSAN trial)	RCT To compare clinical efficacy of rituximab to azathioprine as remission maintenance therapy	500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 plus low-dose prednisone after study entry Daily azathioprine 500mg plus low-dose prednisone until month 22	115 patients (mean age 55; 87 with GPA, 23 with MPA, and 5 with renal-limited ANCA-associated vasculitis) 57 patients on rituximab 58 patients on azathioprine	Relapse rates (the reappearance of disease activity or worsening, with BVAS >0) at month 28 Adverse events at month 60
Pugnet,[26] 2016, France (MAINRITSAN trial)	RCT To compare HRQOL with rituximab to azathioprine as remission maintenance therapy	500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 plus low-dose prednisone after study entry Daily azathioprine 500mg plus low-dose prednisone until month 22	115 patients (mean age 55; 87 with GPA, 23 with MPA, and 5 with renal-limited ANCA-associated vasculitis) 57 patients on rituximab 58 patients on azathioprine	HRQOL (measured with SF-36, with higher score reflects more favourable health state) at month 24 HAQ (to measure the global disability level, with higher score reflects worse disability) at month 24
Terrier,[27] 2018, France (MAINRITSAN trial)	RCT To compare long-term efficacy of rituximab to azathioprine as remission maintenance therapy	500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 plus low-dose prednisone after study entry Daily azathioprine 500mg plus low-dose prednisone until month 22	115 patients (mean age 55; 87 with GPA, 23 with MPA, and 5 with renal-limited ANCA-associated vasculitis) 57 patients on rituximab 58 patients on azathioprine	Relapse rates (the reappearance of disease activity or worsening, with BVAS >0) at month 28 Relapse-free survival rates at month 60 Overall survival rates at month 60 Cumulative concomitant glucocorticoid use at month 60 Adverse events at month 60
Charles,[28] 2018, France (MAINRITSAN 2 trial)	RCT "*To compare individually tailored, based on trimestrial biological parameter monitoring, to fixed-schedule rituximab reinfusion for remission maintenance of antineutrophil cytoplasm*	Fixed rituximab 500mg infusion on days 0 and 14 post-randomisation, then 6, 12 and 18 months, plus low-dose prednisone,	162 patients (mean age 60; 117 with GPA, 45 with MPA) - 81 fixed schedule - 81 individually tailored	Relapse rates (the reappearance of disease activity or worsening, with BVAS >0) at month 28 Infusion rates

First Author, Year, Country	Study Design Objectives	Intervention Comparators	Patients	Main Study Outcomes
	antibody (ANCA)-associated vasculitides (AAVs)" (p 1)	after the first infusion Rituximab 500mg individually tailored, plus low-dose prednisone, at ANCA reappearance or titre increase		

ANCA = antineutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; GPA = granulomatosis with polyangiitis; HAQ = health assessment questionnaire; HRQOL = health-related quality-of-life; MPA = microscopic polyangiitis; RCT = randomized controlled trial; SF-36 = 36-item Short-form Health Survey

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[24]

Strengths	Limitations
Guillevin[25]	
• randomized controlled trial • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • assessor blinded to patient treatment assignment • estimates of random variability and actual probability values provided • power calculation to detect a clinically important effect performed	• patients not blinded to treatment assignment.
Pugnet[26]	
• randomized controlled trial • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • assessor blinded to patient treatment assignment • estimates of random variability and actual probability values provided • power calculation to detect a clinically important effect performed	• patients not blinded to treatment assignment.
Terrier[27]	
• randomized controlled trial • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • assessor blinded to patient treatment assignment • estimates of random variability and actual probability values provided • power calculation to detect a clinically important effect performed	• patients not blinded to treatment assignment.
Charles[28]	
• randomized controlled trial • hypothesis clearly described • method of selection from source population and representation described	• patients not blinded to treatment assignment.

Table 3: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[24]

Strengths	Limitations
• loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • assessor blinded to patient treatment assignment • estimates of random variability and actual probability values provided • power calculation to detect a clinically important effect performed	

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Guillevin[25]	
Relapse rates Rituximab group: 5% (3/57) Azathioprine group: 29% (17/58) *P* = 0.002 *Adverse events* The frequencies of severe adverse events were similar in the two groups. 25 patients in each group had severe adverse events (infections, hematologic events, cancer) (*P* = 0.92) Severe infections: 8 patients (14%) in the azathioprine group 11 (19%) in the rituximab group Hematologic events (leukopenia, anemia) 9 patients (16%) in the azathioprine group 1 (2%) in the rituximab group Cancer: 2 patients (3%) in the azathioprine group 1 (2%) in the rituximab group Death: 2 patients (3%) in the azathioprine group died (1 from sepsis and 1 from pancreatic cancer) 0 patient in the rituximab group	*"More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine"* (p 1771)
Pugnet[26]	
HRQOL (mean changes from baseline of SF-36 score to month 24; high score reflects more favourable health state) Both rituximab and azathioprine improved SF-36 scores from baseline. The physical scores did not differ significantly between the two groups, while patients on azathioprine had better mental scores than patients on rituximab Rituximab group: physical score +3.95 points higher than azathioprine group; *P*=0.067 Azathioprine group: mental score +4.23 points higher than rituximab group; *P*=0.041 *HAQ (mean changes from baseline to month 24; higher score reflects worse disability)*	*"Azathioprine-treated patients for AAV maintenance therapy showed a decline in physical abilities when compared to RTX at M24 in the MAINRITSAN trial" (p S54)*

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Baseline HAQ Azathioprine: 0.33 ± 0.53 Rituximab: 0.24 ± 0.38 Changes from baseline unchanged for rituximab group but worsened significantly for the azathioprine group Rituximab group: 0.16 points lower than the azathioprine group; *P*=0.038	
Terrier[27]	
Relapse rates (HR) The azathioprine versus rituximab HRs were 2.51 (95% CI 1.35 to 4.69) (p=0.003) for major relapses and 2.11 (95% CI 1.19 to 3.73) (p=0.012) for major or minor relapses *Major relapse-free survival rates* Rituximab group: 71.9% (95% CI 61.2% to 84.6%) Azathioprine group: 49.4% (95% CI 38.0% to 64.3%) (*P*=0.003) *Minor and major relapse-free survival rates* Rituximab group: 57.9% (95% CI 46.4% to 72.2%) Azathioprine group: 37.2% (95% CI 26.5% to 52.2%) and (*P*=0.012); *Overall survival rates* Rituximab group: 100% Azathioprine group: 93.0% (95% CI 86.7% to 99.9%) (*P* = 0.045) *Cumulative glucocorticoid use* Similar between the 2 groups *Adverse events* Severe infection: 16 (28%) azathioprine group and 15 (26%) rituximab group (bronchitis and pneumonia) Cardiovascular events: 5 (9%) azathioprine group and 6 (11%) rituximab group Cancer: 6 (10%) azathioprine group (including non-melanoma skin cancer in four) and 2 (4%) prostate cancers rituximab group	*"The rate of sustained remission for ANCA-associated vasculitis patients, following rituximab-based or azathioprine-based maintenance regimens, remained superior over 60 months with rituximab, with better overall survival* " (p 1)
Charles[28]	
Relapse rates Tailored infusion group: 14/81 (17.3%)	*"AAV relapse rates did not differ significantly between individually tailored and fixed schedule rituximab regimens. Individually tailored-arm patients received fewer rituximab*

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Fixed-schedule infusion group: 8/81 (9.9%) (*P*=0.22) Number of infusions Tailored-infusion group: 248 (%) Fixed-schedule group: 381 (%)	*infusions"* (p 1)

AAV = antineutrophil cytoplasmic antibody- associated vasculitis; ANCA = antineutrophil cytoplasmic antibody; HAQ = health assessment questionnaire; HR = hazard ratio; HRQOL = health-related quality-of-life; RTX = rituximab; SF-36 = 36-item Short-form Health Survey