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Comparison of Two Rituximab Induction Regimens for Antineutrophil Cytoplasm Antibody–Associated Vasculitis: Systematic Review and Meta-Analysis

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Objective. The objective of this study was to compare the efficacy and safety of two rituximab (RTX) regimens for the induction of remission in severe antineutrophil cytoplasm antibody–associated vasculitis (AAV): the four-dose (375 mg/m^2 intravenously weekly) versus the two-dose (1000 mg intravenously biweekly) regimen.

Methods. A systematic review was performed to identify studies using the four- and/or two-dose RTX regimens for induction of remission in severe AAV. Disease status 6 months after RTX infusion was required for inclusion. Patients were excluded if they received concomitant cyclophosphamide or plasma exchange. The primary end point was the proportion of patients in complete remission at 6 months. The pooled estimate was obtained by using meta-analysis methods for proportions with random effects. Secondary end points included antineutrophil cytoplasm antibody status, number of patients with B-cell depletion, mean prednisone dose, infections, and death.

Results. A total of 27 studies and 506 patients were included for analysis: 361 patients received the four-dose regimen, and 145 patients received the two-dose regimen. Most patients had relapsing disease at inclusion (83% and 92% of patients, respectively). There was no significant difference between the four- and two-dose regimens, with a complete remission achieved in 85% (95% confidence interval [CI]: 70-96) and 91% (95% CI: 79-99) of patients, respectively. At 6 months, both regimens were associated with a similar mean daily prednisone dose (8.1 mg), infections (12% in both), and death (1% vs 0%, respectively).

Conclusion. No difference was found in terms of efficacy or safety between the four- and two-dose RTX regimens for induction of remission in severe AAV.

INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV), which includes granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), can be organ- and life-threatening. According to recent epidemiological studies, these vasculitides have an annual incidence rate of 10 to 20 cases per million in the United States and Europe (1).

The Canadian Vasculitis Research Network (CanVasc), the European League Against Rheumatism (EULAR), and the European Renal Association━European Dialysis and Transplant Association (ERA-ETDA) recommend both rituximab (RTX) and cyclophosphamide (CYC) as remission induction treatment in patients with GPA or MPA and organ- and/or life-threatening manifestations in combination with glucocorticoids (2-4). RTX is a monoclonal antibody that targets CD20 antigen on B cells, induces

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their apoptosis, and leads to prolonged B-cell depletion lasting up to 6 to 12 months (5-7). Because B cell–derived ANCAs are implicated in the pathogenesis of AAV, their negativity after induction therapy may be associated with a lower risk of relapse (8).

Two large multicenter randomized controlled trials, rituximab for ANCA-associated vasculitis (RAVE) and randomized trial of rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS), studied RTX with an induction dose of 375 mg/m^2 administered intravenously every week for four doses in patients with severe AAV (5,7). The RITUXVAS study compared RTX combined with two initial pulses of CYC with the standard pulse regimen of CYC for induction of remission. The RAVE trial compared RTX with the daily oral regimen of CYC in similar patients with severe AAV. Both trials showed that RTX was not inferior to standard CYC induction treatment, with no significant difference in short-term adverse event rates (5,7,9). Furthermore, RTX efficacy was maintained at 6 and 12 months in the extended follow-up period (3,7,10). On the basis of these trial, the US Food and Drug Administration (FDA) approved in April 2011 the four-dose RTX regimen in combination with glucocorticoids for remission induction in new-onset and relapsing severe GPA and MPA (11).

Because RTX was approved earlier by the FDA for the treatment of rheumatoid arthritis with a regimen of two doses of 1000 mg biweekly, several groups started to use this alternative, which was more practical and convenient for their patients with AAV. Several series in patients with severe newly diagnosed or refractory AAV suggested that this two-dose RTX induction regimen could also be effective in inducing remission (6,12,13,14,15,16,17,18). However, no prospective head-to-head comparative studies of these two regimens have yet been conducted.

The objective of this systematic review and meta-analysis was to assess whether these two RTX regimens, namely the four-dose (375 mg/m^2 weekly for 4 weeks) and two-dose (1000 mg on days 1 and 15) regimens, differ in terms of efficacy and safety for the induction of remission in adult patients with active severe GPA or MPA.

MATERIALS AND METHODS

Study and patient selection. Studies were included if they assessed the efficacy of RTX administered as the four-dose regimen or the two-dose regimen in adult patients with active severe GPA or MPA. Randomized and nonrandomized trials, cohort studies, case-control studies, and case series (defined as studies with more than one case reported) were included. Case reports of single patients, systematic reviews, and meta-analysis were excluded.

In the studies included, only data for patients meeting the following inclusion criteria were collected: 1) adults (18 years or older); 2) presenting with newly diagnosed, relapsing, or refractory GPA or MPA, including unclassified AAV; 3) having severe disease manifestations, defined as any organ- or life-threatening condition requiring induction of remission with RTX; 4) initiated on RTX as the four- or two-dose regimen; 5) having a minimal follow-up of 6 months; and 6) having data on remission status at 6 months. Patients were excluded if they received concomitant CYC and/or plasma exchange for remission induction or if they received RTX therapy to maintain rather than induce remission.

Literature search strategy. PubMed, Cochrane, ClinicalTrials.gov, Google Scholar, Medline, and the Cochrane Central Register of Controlled Trials were searched from January 1, 2000, to October 7, 2019, for studies published in English or French by using a combination of the following Medical Subject Headings terms and keywords: "Granulomatosis with Polyangiitis," "Wegener's Granulomatosis," "Microscopic Polyangiitis," "ANCA-Associated Vasculitis," "Antineutrophil Cytoplasm Antibody-Associated Vasculitis," "AAV," and "Rituximab." Titles and abstracts of studies were screened independently by two reviewers (MZ-N and CF). When eligible or when the title and abstract were insufficient to determine their eligibility, the full text was retrieved and reviewed. Reference lists of all selected studies were manually screened for any additional eligible studies. Although systematic reviews and meta-analysis were not considered for inclusion, their reference lists were similarly screened.

A third reviewer (VB) was involved in case of doubt or disagreement between the two reviewers and reviewed all included studies and determined if all or only a subset of the studies' participants were eligible for analysis according to the prespecified inclusion criteria. In case of uncertainty, the senior supervisor (J-PM) was consulted. In case of uncertainty or to obtain additional information regarding a study, the corresponding author was contacted; studies were excluded if the required information was not provided.

Data extraction. One author (VB) extracted and collected, in a standardized form, the following information for each included study: first author, name of journal, year of publication, country of study, study type, number of centers involved, number of enrolled patients, type of RTX induction regimen, definition of complete and partial remission, definition of treatment nonresponse, and definition of relapse.

Individual data on included patients also involved baseline demographic and clinical characteristics, such as the following: sex, age at RTX therapy, type of vasculitis (GPA, MPA, or unclassified AAV; new diagnosis or relapse), ANCA positivity, ANCA type (proteinase 3 ANCA or myeloperoxidase ANCA) as measured by enzyme-linked immunosorbent assays, disease activity as assessed by the Birmingham Vasculitis Activity Score (BVAS) version 1 or 3 or the BVAS for Wegener Granulomatosis (BVAS/WG), time from diagnosis to RTX therapy, cumulative previous exposition to CYC, disease response at 6 months (remission or nonresponse), and adverse events (infections and deaths).

Quality assessment and publication bias. Two authors (VB and J-PM) independently assessed risk of bias for each study using study design–specific tools. The Cochrane Collaboration's tool, adapted from Higgins et al (19), was used for assessing risk

of bias in randomized trials. For case series and descriptive cohort studies, an ad hoc 10-item scale adapted from the evaluation tool of Murad et al (20) and from the Joanna Briggs Institute evaluation tool of Munn et al (21), was used to assess the methodological quality of these studies (Supplementary Table 1).

Outcomes. The primary outcome was the proportion of complete remission at 6 months in patients with severe GPA or MPA receiving either the four- or two-dose RTX regimen for induction therapy. Complete remission was defined as a BVAS of 0 and/

or as the absence of disease activity on clinical assessment, as defined in each study. Secondary outcomes at 6 months included the number of patients with positive and negative ANCA, the number of patients with B-cell depletion, the mean disease activity score (BVAS version1 or 3 or BVAS/WG), the mean daily dose of prednisone (or equivalent), and the mean time to remission after induction therapy with RTX.

Safety outcomes at 6 months included the proportion of patients with infection(s) and the number of deaths in each RTX treatment group.
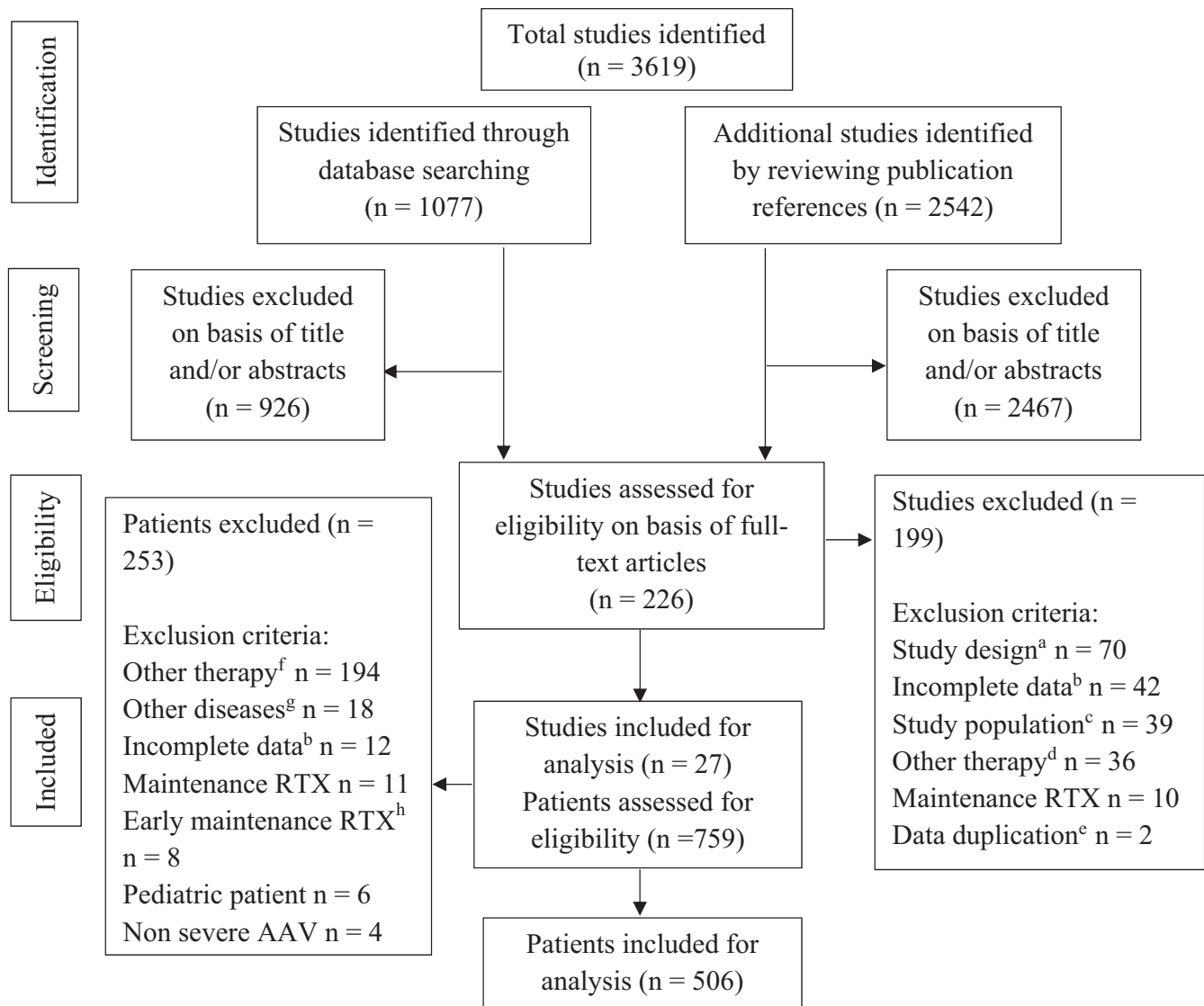
Figure 1. Four-phase flowchart of included and excluded studies for the meta-analysis. [a]Excluded study designs were society recommendations, systematic reviews, meta-analyses, single case reports, and pharmacokinetic trials. [b]Trials and patients with incomplete data concerning the primary efficacy outcome of remission at 6 months following rituximab (RTX). [c]Patients with nonsevere antineutrophil cytoplasm antibody–associated vasculitis (AAV) (n = 1), pediatric patients (n = 3), and patients with inflammatory or autoimmune diseases other than AAV (n = 35). [d]All induction therapies other than the four- and two-dose RTX regimens: other doses of RTX (n = 17), combination of RTX and cyclophosphamide (n = 11), medications other than RTX (n = 6), atypical dosing of glucocorticoids (n = 2). [e]Studies were excluded because they reported the outcomes of subgroups of patients from studies already included in our analysis. [f]Induction therapies other than the four- and two-dose rituximab regimens were excluded: medications other than RTX (n = 103), combination of RTX and cyclophosphamide and/or plasma exchange (n = 81), other doses of RTX (n = 10). [g]Other diseases involved lupus (n = 11) and other vasculitides (n = 7). [h]Patients initiated on RTX maintenance therapy before the 6 months post induction infusion were excluded.

Statistical analysis. The proportion of patients with complete remission in each study was analyzed by using the metaprop command in Stata version 11 (StataCorp LLC). Meta-analyses were stratified according to the two RTX induction regimens. Random effects were used when significant heterogeneity was found (I^2 P < 0.05).

For the primary outcome, we conducted two sensitivity analyses by excluding 1) studies with poor methodological quality (at high risk of bias) and 2) studies that were not randomized controlled trials.

RESULTS

Of the 3619 studies identified, 226 full-text articles were assessed for eligibility and 27 met inclusion criteria for analysis (Figure 1). Of note, 9 of the 27 trials were included after their authors clarified and shared additional data on their patients and remission outcomes. We included 13 case series, 9 retrospective cohort studies, 4 prospective cohort studies, and 1 randomized controlled trial. Four of the twenty-seven studies were considered of low quality: three involving the four-dose RTX regimen and one involving the two-dose RTX regimen. Most studies were monocentric and conducted in Northern European countries or in the United States (Table 1 and 2). Thirteen studies used the four-dose RTX regimen, seven studies used the two-dose RTX regimen, and seven studies used both regimens for remission induction in AAV. These 27 studies contributed data for 759 patients, of whom 253 were excluded according to the prespecified criteria detailed in Figure 1. A total of 506 patients were included in the meta-analysis: 361 in the four-dose AAV RTX group and 145 in the two-dose rheumatoid arthritis RTX group.

Baseline characteristics of patients were similar between the two groups (Table 3). Overall, the mean age at RTX therapy was 50 years, 51% of patients were women, 91% had GPA, 8% had MPA, and the mean time from diagnosis to RTX therapy was 6 years. Relapsing disease at inclusion accounted for 83% and 92% of patients in the four- and two-dose regimen groups, respectively. Eighty-five percent of patients were ANCA-positive at baseline (88% in the four-dose regimen group vs 77% in the two-dose group). The BVAS (version 3) was available for 196 of the 506 included patients, who had a mean score of 10 of 63 in the four-dose RTX group and 9 of 63 in the two-dose RTX group.

The overall percentage of complete remission at 6 months was 88%, with significant heterogeneity (I^2 = 73%; P < 0.001; Figure 2). No significant difference in this percentage was found between the four- and two- regimens (85% [95% confidence interval (CI): 70-96] vs 91% [95% CI: 79-99]; P = 0.376). The magnitude effect in each group was similar after we excluded studies with poor methodological quality (83% for the four-dose regimen vs 90% for the two-dose regimen; P = 0.387; Supplementary Figure 1). However, when limited to the randomized controlled trial only, the magnitude effect was lower, with a complete remission

rate of 71% in the four-dose regimen group (Supplementary Figures 2 and 3).

As for secondary efficacy outcomes, both regimens had similar proportions of patients with positive ANCA levels and B-cell depletion at 6 months (Table 4). The mean daily prednisone doses at 6 months were 7.8 and 8.7 mg in patients treated with the four- and two-dose regimens, respectively. Data on the daily prednisone dose taken at 6 months were available for 125 patients (six studies) in the four-dose RTX group and 56 patients (six studies) in the two-dose RTX group. Because of small sample size, firm conclusions could not be drawn for the secondary efficacy outcomes ANCA status, proportion of patients with B-cell depletion, and mean prednisone dose at 6 months. Moreover, because of insufficient data, we were unable to compare the BVAS score at 6 months (BVAS version 1 or 3 or BVAS/WG) and the mean time to remission following induction with RTX.

At 6 months, the mortality rate (1% in the four-dose RTX group vs 0% in the two-dose RTX group) and the proportion of patients with infection(s) (12% in both groups) were similar between the two RTX regimens (Table 4).

DISCUSSION

In this meta-analysis, there was no significant difference in terms of efficacy and safety at 6 months between the four- and two-dose RTX regimens for induction of remission in patients with severe GPA or MPA. This finding supports the current use of either regimen in clinical practice (2,4).

To our knowledge, no prospective comparative trials between the two regimens has been conducted to compare the four-dose regimen and the two-dose regimen for the induction of remission in AAV. Only the four-dose regimen has been studied in randomized controlled trials. In 2009, a multicentric retrospective cohort study of 58 patients with refractory AAV found similar remission rates between the four- and two-dose regimens (81% and 75%, respectively) (6). However, the interpretation of these results was limited by the small number of patients and by the fact that 40% of patients, whom were unevenly distributed between the two groups, were concomitantly treated with CYC.

In our thorough systematic literature review, more than 3500 trials were screened for inclusion. This search permitted us to study a total of 506 patients, even after those receiving concomitant CYC and/or plasma exchange were excluded to limit possible confounders. Plasma exchange can influence RTX levels, especially if performed shortly and repeatedly after infusions. Because the timing of plasma exchange was variable regarding RTX therapy or unavailable in most studies, excluding these patients was warranted to avoid variability that may affect RTX exposure. Patient baseline characteristics were well balanced between the two treatment groups, including disease activity and proportion of patients with relapsing disease (who represented most of the studied population), such that our findings are less likely

Table 1. Characteristics of included studies using the two-dose rituximab induction regimen

Study: author, country, year	Design	Quality	AAV subtype	Clinical presentation	Disease course	CR definition	Patients, n	CR, n (%)
Ayan et al (27), Turkey, 2018	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	No activity and GC ≤10 mg	17	14 (82)
Charles et al (28), France, 2014	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	No activity on stable maintenance therapy	13	9 (69)
Chocova et al (29), Csech Republic, 2015	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	BVAS V3 = 0	5	3 (60)
Dalkilic et al (18), Turkey, 2012	Case series	Low	GPA	ENT,[a] Syst	Relapsing	No activity	2	2 (100)
Ebrahimiadib et al (30), United States, 2016	Case series	High	GPA	Ocular,[a] Syst	Relapsing	No ocular activity without GC	8	8 (100)
Gregersen et al (13), Denmark, 2013	Case series	High	GPA, MPA	Syst	New + relapsing	BVAS = 0 (unknown version) and GC ≤10 mg	8	8 (100)
Joshi et al (16), United Kingdom, 2011	Retrospective cohort	High	GPA	Ocular,[a] Syst	Relapsing	No activity on stable maintenance therapy and GC ≤7.5 mg	16	16 (100)
Md Yusof et al (17), United Kingdom, 2015	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	BVAS V3 = 0	35	20 (57)
Puéchal et al (31), France, 2019	Retrospective cohort	High	GPA	Syst	New + relapsing	BVAS V3 = 0	18	15 (83)
Recillas-Gispert et al (14), Mexico, 2015	Case series	High	GPA	Ocular,[a] Syst	Relapsing	No ocular activity on stable maintenance therapy	5	4 (80)
Rees F et al (32), United Kingdom, 2011	Case series	High	GPA	Syst	Relapsing	BVAS V3 = 0	2	2 (100)
Shah et al (33), Sweden, United Kingdom, United States, 2015	Retrospective cohort	High	GPA, MPA	Kidney,[a] Syst	New + relapsing	Stable or better eGFR, no hematuria, and no signs of systemic vasculitis for 1 month	4	4 (100)
Smith et al (15), United Kingdom, 2006	Prospective cohort	High	GPA, MPA	Syst	Relapsing	BVAS V1 = 0	4	4 (100)
Taylor et al (12), United Kingdom, 2009	Case series	High	GPA	Ocular,[a] Syst	Relapsing	No ocular activity on stable maintenance therapy and GC ≤7.5 mg	4	4 (100)

Abbreviations: AAV, antineutrophil cytoplasm antibody–associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; CR, complete remission; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; GC, glucocorticoids (prednisone dose equivalent); GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; Syst,: systemic vasculitis with multiorgan involvement; VI, version 1; V3, version 3.
[a] This affected organ drove the indication for induction therapy.

Table 2. Characteristics of included studies using the four-dose rituximab induction regimen

Study: author, country, year	Design	Quality	AAV subtype	Clinical presentation	Disease course	CR definition	Patients, n	CR, n (%)
Ayan et al (27), Turkey, 2018	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	No activity and GC ≤10 mg	2	2 (100)
Cartin-Ceba et al (34), United States, 2012	Retrospective cohort	High	GPA	Syst	Relapsing	BVAS/WG = 0 and no steroids	53	53 (100)
Charles et al (28), France, 2014	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	No activity on stable maintenance therapy	39	20 (51)
Chocova et al (29), Czech Republic, 2015	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	BVAS V3 = 0	1	0 (0)
Geetha et al (35), United States, 2007	Case series	Low	GPA	Syst, post-KTX	Relapsing	No activity and GC ≤10 mg	2	2 (100)
Henes et al (36), Germany, 2007	Case series	High	GPA	Syst	Relapsing	BVAS/WG = 0	6	5 (83)
Keogh et al (37), United States, 2005	Case series	High	GPA	Syst	Relapsing	BVAS/WG = 0	6	6 (100)
Keogh et al (38), United States, 2006	Prospective cohort	High	GPA, MPA	Syst	Relapsing	BVAS/WG = 0	10	10 (100)
Lovric et al (39), Germany, 2009	Case series	High	GPA, MPA	Syst	Relapsing	BVAS V1 = 0	13	5 (38)
Miloslavsky et al (40), Netherlands, United States, 2014	Prospective cohort post-RCT	High	GPA, MPA	Syst	Relapsing	BVAS/WG = 0 and GC ≤10 mg	26	17 (65)
Omdal et al (41), Norway, 2005	Case series	Low	GPA	Syst	Relapsing	No activity on minimal GC doses (≤5 mg: 2 patients, unknown: 1 patient)	3	2 (67)
Oristrell et al (42), Spain, 2009	Case series	Low	GPA	Syst	Relapsing	BVAS/WG = 0	2	2 (100)
Puéchal et al (31), France, 2019	Retrospective cohort	High	GPA	Syst	Both	BVAS V3 = 0	79	69 (87)
Pullerits et al (43), Sweden, 2012	Retrospective cohort	High	GPA, MPA	Syst	Relapsing	No activity on stable maintenance therapy	5	2 (40)
Rees et al (32), United Kingdom, 2011	Case series	High	GPA	Syst	Relapsing	BVAS V3 = 0	2	2 (100)
Shah et al (33), Sweden, United Kingdom, United States, 2015	Retrospective cohort	High	GPA, MPA	Kidney;[a] Syst	Both	Stable or better eGFR, no hematuria, and no signs of systemic vasculitis for 1 month	4	4 (100)
Stasi et al (44), Italy, 2006	Prospective cohort	High	GPA, MPA	Syst	Relapsing	BVAS/WG = 0	6	6 (100)
Stone et al (7), Netherlands, United States, 2010	RCT	High	GPA, MPA	Syst	Both	BVAS/WG = 0 and GC ≤10 mg	99	70 (71)

Abbreviations: AAV, antineutrophil cytoplasm antibody–associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener Granulomatosis; CR, complete remission; eGFR, estimated glomerular filtration rate; GC, glucocorticoids (prednisone dose equivalent); GPA, granulomatosis with polyangiitis; KTX, kidney transplant; MPA, microscopic polyangiitis; RCT, randomized controlled trial; Syst, systemic vasculitis with multiorgan involvement; VI, version 1; V3, version 3.
[a] This affected organ drove the indication for induction therapy.

Table 3. Baseline characteristics in patients treated with two different rituximab induction regimens

	All patients	Rituximab 375 mg/m^2 weekly (four doses)	Rituximab 1000 mg biweekly (two doses)
N	506	361	145
Age at rituximab treatment	n = 240	n = 143	n= 97
Weighted mean, years	50	50	49
Sex	n = 428	n = 296	n = 132
Female, n (%)	220 (51)	148 (50)	72 (55)
Vasculitis type	n = 457	n = 355	n = 102
Granulomatosis with polyangiitis, n (%)	415 (91)	321 (90)	94 (92)
Microscopic polyangiitis, n (%)	38 (8)	33 (9)	5 (5)
AAV unclassified, n (%)	4 (1)	1 (0)	3 (3)
Vasculitis course	n = 506	n = 361	n = 145
Relapsing, n (%)	433 (86)	300 (83)	133 (92)
New diagnosis, n (%)	73 (14)	61 (17)	12 (8)
Time since diagnosis to first rituximab infusion	n = 263	n = 171	n = 92
Weighted mean, years	6	6	5
Cyclophosphamide exposure before rituximab treatment	n = 225	n = 132	n = 93
Weighted mean, g	23	23	18
Disease activity score			
BVAS/WG	n = 140	n = 134	n = 6
Weighted mean	8	8	17
BVAS V3	n = 196	n = 121	n = 75
Weighted mean	10	10	9
ANCA statusa	n = 462	n = 345	n = 117
ANCA-positive patients, n (%)	394 (85)	304 (88)	90 (77)
ANCA-negative patients, n (%)	68 (15)	41 (12)	27 (23)
ANCA type[a]	n = 363	n = 304	n = 59
PR3-ANCA, n (%)	307 (74)	259 (85)	48 (81)
MPO-ANCA, n (%)	56 (13)	45 (14)	11 (19)

Abbreviations: AAV, antineutrophil cytoplasm autoantibody–associated vasculitis; ANCA, antineutrophil cytoplasm autoantibody; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener Granulomatosis; BVAS/V3, Birmingham Vasculitis Activity Score version 3; MPO-ANCA, myeloperoxidase antineutrophil cytoplasm autoantibody; PR3-ANCA, proteinase 3 antineutrophil cytoplasm autoantibody.
[a] Measured by enzyme-linked immunosorbent assay.

to be attributed to differences between the two groups. Safety outcomes (death and infections) at 6 months were also similar between the two groups. Although data were insufficient to conclude on secondary efficacy outcomes, many patients became ANCA-negative at 6 months, and more than 70% of patients achieved B-cell depletion in both groups.

There are several relevant socioeconomic implications arising from these results. For instance, in Canada, for an average patient measuring 170 cm and weighing 80 kg, the total RTX induction dose would be 3000 mg with the four-dose regimen, compared to 2000 mg with the two-dose regimen, which would represent one third of cost-sparing (22). In patients with obesity, the dose and cost can be twice as high with the four-dose regimen compared to the two-dose regimen. Considering that obesity has dramatically increased worldwide in the past few years (23), it should be cost-effective to determine whether the two RTX regimens are equivalent in terms of efficacy and safety in patients with overweight. Furthermore, weekly infusions for 1 month involves additional fees related to repeat administration of the medication and is more time consuming for patients and health care professionals.

Our study suggests that a lower two-dose regimen may be as effective as a four-dose regimen to induce remission in patients with severe AAV. In fact, because no dose-escalation study was performed to determine the optimal RTX dosing, lower doses may be adequate in this setting. For instance, several observational studies reported high rates of clinical remission and B-cell depletion in patients with AAV with induction RTX doses lower than or equal to 1000 mg (24,25). In a retrospective trial of 12 patients with refractory GPA, 11 patients achieved remission and all had complete B-cell depletion with a median RTX induction dose of 1000 mg only (24). Even though the minimal RTX dose needed to achieve remission in severe AAV remains uncertain, these findings reinforce the plausibility of our results.

Our study has several limitations. A selection bias remains possible given that potentially eligible studies were excluded when published in languages other than English or French and when information required to assess their eligibility could not be provided. In the former case, it might have led to underrepresentation of patients from other ethnic groups, such as Asian patients. In addition, our meta-analysis mainly included observational studies, which are susceptible to bias. However, the remission rate in both RTX regimens was similar after exclusion of studies of poor methodological quality. Because AAV is a rare disease (1), randomized controlled trials on the subject are scant. Thus, only the RAVE trial fulfilled the criteria for inclusion in our meta-analysis. Although the RAVE trial's complete remission rate of 71 % (95%
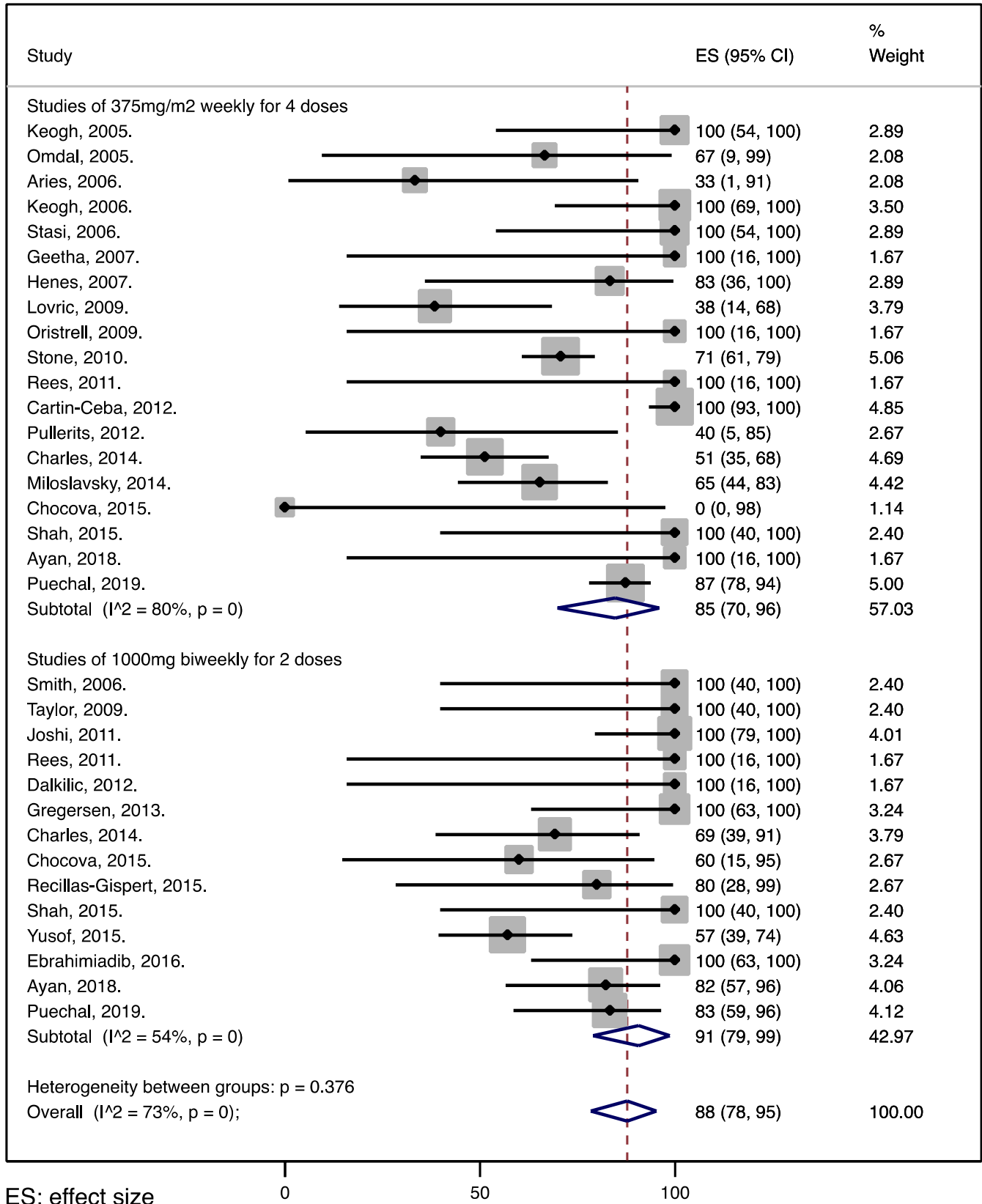
Study		ES (95% CI)	% Weight
Studies of 375mg/m2 weekly for 4 doses			
Keogh, 2005.		100 (54, 100)	2.89
Omdal, 2005.		67 (9, 99)	2.08
Aries, 2006.		33 (1, 91)	2.08
Keogh, 2006.		100 (69, 100)	3.50
Stasi, 2006.		100 (54, 100)	2.89
Geetha, 2007.		100 (16, 100)	1.67
Henes, 2007.		83 (36, 100)	2.89
Lovric, 2009.		38 (14, 68)	3.79
Oristrell, 2009.		100 (16, 100)	1.67
Stone, 2010.		71 (61, 79)	5.06
Rees, 2011.		100 (16, 100)	1.67
Cartin-Ceba, 2012.		100 (93, 100)	4.85
Pullerits, 2012.		40 (5, 85)	2.67
Charles, 2014.		51 (35, 68)	4.69
Miloslavsky, 2014.		65 (44, 83)	4.42
Chocova, 2015.		0 (0, 98)	1.14
Shah, 2015.		100 (40, 100)	2.40
Ayan, 2018.		100 (16, 100)	1.67
Puechal, 2019.		87 (78, 94)	5.00
Subtotal ($I^2 = 80\%$, p = 0)		85 (70, 96)	57.03
Studies of 1000mg biweekly for 2 doses			
Smith, 2006.		100 (40, 100)	2.40
Taylor, 2009.		100 (40, 100)	2.40
Joshi, 2011.		100 (79, 100)	4.01
Rees, 2011.		100 (16, 100)	1.67
Dalkilic, 2012.		100 (16, 100)	1.67
Gregersen, 2013.		100 (63, 100)	3.24
Charles, 2014.		69 (39, 91)	3.79
Chocova, 2015.		60 (15, 95)	2.67
Recillas-Gispert, 2015.		80 (28, 99)	2.67
Shah, 2015.		100 (40, 100)	2.40
Yusof, 2015.		57 (39, 74)	4.63
Ebrahimiadib, 2016.		100 (63, 100)	3.24
Ayan, 2018.		82 (57, 96)	4.06
Puechal, 2019.		83 (59, 96)	4.12
Subtotal ($I^2 = 54\%$, p = 0)		91 (79, 99)	42.97
Heterogeneity between groups: p = 0.376			
Overall ($I^2 = 73\%$, p = 0);		88 (78, 95)	100.00

ES: effect size

0   50   100

Figure 2. Percentage of complete remission according to the rituximab dosing regimen. CI, confidence interval; ES, effect size.

Table 4. Secondary efficacy and safety outcomes at 6 months in patients treated with two different rituximab induction regimens

	All patients	Rituximab 375 mg/m^2 weekly (four doses)	Rituximab 1000 mg biweekly (two doses)
N	506	361	145
ANCA status[a]	n = 223	n = 200	n = 23
ANCA-positive patients, n (%)	95 (43)	87 (44)	8 (35)
ANCA-negative patients, n (%)	128 (57)	113 (57)	15 (65)
ANCA type[a]	n = 44	n = 36	n = 8
PR3-ANCA, n (%)	40 (91)	34 (94)	6 (75)
MPO-ANCA, n (%)	4 (9)	2 (6)	2 (25)
Patients with B-cell depletion	n = 225	n = 204	n = 21
n (%)	179 (80)	164 (80)	15 (71)
Prednisone dose	n = 181	n = 125	n = 56
Weighted mean	8.1	7.8	8.7
Patients with infections	n = 306	n = 215	n = 91
n (%)	36 (12)	25 (12)	11 (12)
Deaths	n = 423	n = 278	n = 145
n (%)	4 (1)	4 (1)	0 (0)

Abbreviations: ANCA, antineutrophil cytoplasm autoantibody; MPO-ANCA, myeloperoxidase antineutrophil cytoplasm autoantibody; PR3-ANCA, proteinase 3 antineutrophil cytoplasm autoantibody.
[a] Measured by enzyme-linked immunosorbent assay.

CI: 61-79) is nonsignificantly lower than the one of 86% (95% CI: 69-98) reported in observational studies, the magnitude effect of RTX therapy may have been overestimated in the observational study design. We also observed significant heterogeneity between studies. Despite several sensitivity and subgroup analyses, we were unable to identify the major source of variation. We hypothesize that the multiple study designs with their different target populations and sources of bias, the numerous clinical manifestations of AAV requiring induction therapy, and the differences in the definitions of complete remission probably all contributed to this heterogeneity. Moreover, we were unable to compare levels of immunoglobulin G (IgG) between the two RTX regimens because of insufficient data in the included studies. Further studies are needed to characterize variations in IgG levels with these two RTX regimens and formally assess whether a lower dose reduces the risk of infection in the setting of AAV induction therapy. Finally, it is unknown whether the effect of the different regimens would have remained similar beyond 6 months.

As for the external validity of our review, most included patients were from Northern Europe and North America and had severe relapsing GPA. Thus, it is uncertain whether both regimens are as equivalent in terms of efficacy and safety in MPA, new-onset AAV, and patients from other ethnic groups. However, the clinical phenotype (GPA vs MPA) may predominantly affect the risk of relapse during follow-up, with more frequent relapsing disease in patients with GPA. Also, in the RAVE trial, a similar proportion of remission was achieved with rituximab in patients with GPA and MPA (7). Therefore, although we had more patients with GPA in our study, using the two-dose induction regimen in patients with MPA is reasonable. Finally, the exclusion of patients treated concomitantly with plasma exchange might have led to selection of patients with less severe disease. However, this is unlikely given that most patients included in our study had long-lasting disease refractory to numerous immunosuppressors. In addition, the recent plasma exchange and glucocorticoids for treatment of ANCA-associated vasculitis trial did not show any benefits of plasma exchange in terms of death, end-stage kidney disease, sustained remission rates, and adverse events (26).

No difference was found in terms of efficacy and safety between the four- and two-dose RTX regimens for induction of remission in patients with severe AAV. A head-to-head comparison of both regimens in a randomized controlled trial would ultimately be needed to confirm these results. Areas of uncertainty also remain concerning the optimal dosage in patients with obesity, in patients with new-onset AAV or MPA, and in other ethnic groups, all of whom were underrepresented in our meta-analysis population.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Bénard and Makhzoum had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Bénard, Durand, Pagnoux, Makhzoum.
Acquisition of data. Bénard, Farhat, Zarandi-Nowroozi, Charles, Puéchal, Guillevin, Makhzoum.

Analysis and interpretation of data. Bénard, Durand, Pagnoux, Makhzoum.

REFERENCES

1. Shi L. Anti-neutrophil cytoplasmic antibody-associated vasculitis: prevalence, treatment, and outcomes. Rheumatoly Int 2017;37:1779–88.

2. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.

3. Makhzoum J-P, Pagnoux C. Actualités thérapeutiques de la granulomatose avec polyangéite (Wegener) et de la polyangéite microscopique. Revue du Rhumatisme Monographies 2017;84:242–8.

4. Mendel A, Ennis D, Go E, Bakowsky V, Baldwin C, Benseler SM, et al. CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis: 2020 update. J Rheumatol 2020. E-pub ahead of print.

5. Jones RB, Cohen Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.

6. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009;60:2156–68.

7. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.

8. Sanders J-S, Huitma MG, Kallenberg CG, Stegeman CA. Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. Rheumatology (Oxford) 2006;45:724–9.

9. Jones RB, Furuta S, Cohen Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis 2015;74:1178–82.

10. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417–27.

11. Clain JM, Cartin-Ceba R, Fervenza FC, Specks U. Experience with rituximab in the treatment of antineutrophil cytoplasmic antibody associated vasculitis. Ther Adv Musculoskelet Dis 2014;6:58–74.

12. Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. Arthritis Rheum 2009;60:1540–7.

13. Gregersen JW, Chaudhry A, Jayne DR. Rituximab for ANCA-associated vasculitis in the setting of severe infection. Scand J Rheumatol 2013;42:207–10.

14. Recillas-Gispert C, Serna-Ojeda JC, Flores-Suárez LF. Rituximab in the treatment of refractory scleritis in patients with granulomatosis with polyangiitis (Wegener's). Graefes Arch Clin Exp Ophthalmol 2015;253:2279–84.

15. Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. Arthritis Rheum 2006;54:2970–82.

16. Joshi L, Taylor SR, Salama A, Shirodkar A-L, Pusey C, Lightman S. Rituximab in refractory ophthalmic Wegener's granulomatosis: PR3 titers predict relapse, but repeat treatment is effective [abstract]. Invest Ophthalmol Vis Sci 2011;52:4252.

17. Md Yusof MY, Vital EM, Das S, Dass S, Arumugakani G, Savic S, et al. Repeat cycles of rituximab on clinical relapse in ANCA-associated vasculitis: identifying B cell biomarkers for relapse to guide retreatment decisions. Ann Rheum Dis 2015;74:1734–8.

18. Dalkilic E, Alkis N, Kamali S. Rituximab as a new therapeutic option in granulomatosis with polyangiitis: a report of two cases. Mod Rheumatol 2012;22:463–6.

19. Higgins JT, Altman DG, Gøtzsch PC, Jüni P, Moher D, Oxman AD. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

20. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60–3.

21. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Evid Synth 2020;18:2127–33.

22. Bibilothèque et Archives nationales du Québec. Liste des médicaments. 2020. URL: https://www.ramq.gouv.qc.ca/sites/default/files/documents/liste-med-2020-07-08-fr.pdf.

23. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766–81.

24. Wawrzycka-Adamczyk K, Zugaj A, Wludarczyk A, Kosalka J, Sznajd J, Bazan-Socha S, et al. Lower doses of rituximab in remission induction for refractory granulomatosis with polyangiitis. Przegl Lek 2014;71:663–5.

25. Saito A, Takeuchi Y, Kagaya S, Ojima Y, Fukami H, Sato H, et al. Remission induction therapy with rituximab for microscopic polyangiitis: a feasibility study. Tohoku J Exp Med 2017;242:53–62.

26. Walsh M, Merkel PA, Peh C-A, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622–31.

27. Ayan G, Esatoglu SN, Hatemi G, Ugurlu S, Seyahi E, Melikoglu M, et al. Rituximab for anti-neutrophil cytoplasmic antibodies-associated vasculitis: experience of a single center and systematic review of non-randomized studies. Rheumatol Int 2018;38:607–22.

28. Charles P, Neel A, Tieulie N, Hot A, Pugnet G, Decaux O, et al. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. Rheumatology (Oxford) 2014;53:532–9.

29. Chocova Z, Hruskova Z, Mareckova H, Svobodova B, Duskova D, Bednarova V, et al. Rituximab use in patients with ANCA-associated vasculitis: clinical efficacy and impact on immunological parameters. Clin Rheumatol 2015;34:107–15.

30. Ebrahimiadib N, Modjtahedi BS, Roohipoor R, Anesi SD, Foster CS. Successful treatment strategies in granulomatosis with polyangiitis-associated peripheral ulcerative keratitis. Cornea 2016;35:1459–65.

31. Puéchal X, Iudici M, Calich AL, Vivot A, Terrier B, Regent A, et al. Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients. Rheumatology (Oxford) 2019;58:401–9.

32. Rees F, Yazdani R, Lanyon P. Long-term follow-up of different refractory systemic vasculitides treated with rituximab. Clin Rheumatol 2011;30:1241–5.

33. Shah S, Hruskova Z, Segelmark M, Morgan MD, Hogan J, Lee SK, et al. Treatment of severe renal disease in ANCA positive and negative small vessel vasculitis with rituximab. Am J Nephrol 2015;41:296–301.

34. Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sanchez-Menendez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum 2012;64:3770–8.

35. Geetha D, Seo P, Specks U, Fervenza FC. Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis post-kidney transplant: report of two cases. Am J Transplant 2007;7:2821–5.

36. Henes JC, Fritz J, Koch S, Klein R, Horger M, Risler T, et al. Rituximab for treatment-resistant extensive Wegener's granulomatosis–additive effects of a maintenance treatment with leflunomide. Clin Rheumatol 2007;26:1711–5.

37. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:262–8.

38. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006;173:180–7.

39. Lovric S, Erdbruegger U, Kumpers P, Woywodt A, Koenecke C, Wedemeyer H, et al. Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients. Nephrol Dial Transplant 2009;24:179–85.

40. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Rituximab for the treatment of relapses in antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2014;66:3151–9.

41. Omdal R, Wildhagen K, Hansen T, Gunnarsson R, Kristoffersen G. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response. Scand J Rheumatol 2005;34:229–32.

42. Oristrell J, Bejarano G, Jordana R, Monteagudo M, Marí B, Casanovas A, et al. Effectiveness of rituximab in severe Wegener's granulomatosis: report of two cases and review of the literature. Open Respir Med J 2009;3:94–9.

43. Pullerits R, Ljevak M, Vikgren J, Bokarewa M. Off-trial evaluation of the B cell-targeting treatment in the refractory cases of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: long-term follow-up from a single centre. Scand J Immunol 2012;76:411–20.

44. Stasi R, Stipa E, Del Poeta G, Amadori S, Newland AC, Provan D. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Rheumatology 2006;45:1432–6.