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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Rituximab Maintenance Therapy for the Treatment and Management of Rheumatoid Arthritis: A Review of Clinical Effectiveness

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Context and Policy Issues

Rheumatoid arthritis is an autoimmune, chronic inflammatory, disorder that targets the membranes of joints, causing joints to become tender, warm, swollen, and stiff.[1] The disease may also affect other systems in the body, such as skin, eyes, lungs, heart, and blood vessels.[1] Rheumatoid arthritis varies in severity, with periods of disease remission followed by flares.[1] Both genetic and environmental factors have etiological roles and women are more likely to develop the disease than men.[1] In Canada, about one in every 100 adults has rheumatoid arthritis.[2]

The treatment modalities for rheumatoid arthritis aim to slow disease progression and maintain remission. These goals may be achieved with disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, or biologic agents.[1] The biologic agents target the immune system to prevent the inflammatory response, and they may be administered concomitantly with DMARDs. One type of biologic, rituximab, is a chimeric monoclonal antibody that binds to CD20 on B-cells and may be administered to adults with rheumatoid arthritis when biologics that target tumour necrosis factor α (i.e. TNF-α blockers) fail.[3] Rituximab is administered as an initial two-dose intravenous infusion, two weeks apart. Based on the product monograph, it can be repeated every six months, however no sooner than every four months.[3]

The coverage of rituximab, under the various government-sponsored drug plans, includes a maximum of two courses per year; rituximab is not currently reimbursed for maintenance treatment. In 2007, the Canadian Agency for Drugs and Technologies in Health reviewed rituximab under the Common Drug Review.[4] Rituximab was given a positive recommendation, however the Committee noted that the evidence for repeated doses was insufficient and that retreatment should be considered only in patients who achieved a response followed by a loss of effect.[4] Clinicians would like to prescribe rituximab to patients, prior to a flare or loss of effect. Therefore, a review of the evidence is needed to support the administration of rituximab as regularly scheduled therapy to maintain remission or low disease activity in patients with moderate to severe rheumatoid arthritis.

Research Question

What is the clinical effectiveness of rituximab maintenance therapy for the treatment and management of rheumatoid arthritis?

Key Findings

Five non-randomized studies were included in this review, of which three were single-arm studies and two were comparative cohorts. The studies were of poor quality overall, many with small sample sizes, no comparator group, large number of patient drop-outs, and the presence of differences in baseline characteristics among groups within studies. The studies were also hampered by incomplete reporting, such as not specifying whether patients had responded to an initial cycle of rituximab infusion prior to receiving maintenance therapy, the number of rituximab cycles received, or the maintenance doses of rituximab administered. Furthermore, the applicability of the evidence base to Canadian rheumatology practice settings is unclear because all studies were conducted in other countries.

In a large comparative study (N = 800) that compared fixed interval rituximab retreatment versus on-flare retreatment up to a total of three cycles, the Disease Activity Score 28 (DAS28) improvement from the start of therapy was statistically greater for the fixed interval group after both first and second retreatments. However, the results of this study must be interpreted with caution due to the potential for confounding by indication. Another, smaller, comparative study (N = 102) found no statistically significant differences in efficacy outcomes. The single-arm studies examined rituximab maintenance infusion on remission, DAS28, and safety.

Based on the evidence reviewed, the relative benefits and safety of rituximab maintenance therapy compared with flare-based retreatment are unclear and more comparative studies are needed reduce uncertainty.

Methods

Literature Search Methods

A limited literature search, with main concepts appearing in title or major subject heading, was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main search to limit retrieval by publication type. A second broader search was also conducted with main concepts appearing in the title, abstract or subject heading. A methodological filter was applied to the broader search to limit retrieval to health technology assessments, systematic reviews and meta-analyses. For both searches, retrieval was limited to the human population where possible and English-language documents published between January 1, 1997 and May 30, 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 (adults and children) with moderate to severe rheumatoid arthritis who have taken at least one dose of rituximab and have had a response to the treatment.
Intervention	Rituximab at any dose given at regular intervals as maintenance therapy.
Comparator	Rituximab given at a disease flare or increased disease activity Another drug as maintenance therapy No comparator
Outcomes	Effectiveness: Disease activity, remission, joint count, function, patient-reported outcomes such as pain, fatigue, HRQL Safety: Infections, other adverse events
Study Designs	Health technology assessments, systematic reviews, meta-analyses Randomized controlled trials Non-randomized studies

HRQL = health-related quality of life; mg = milligram

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were available as abstracts or journal letters only, or were published prior to 1997.

Critical Appraisal of Individual Studies

The included non-randomized studies were critically appraised using the Downs and Black checklist.[5] 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 738 citations were identified in the literature search. Following screening of titles and abstracts, 708 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 27 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

The five studies were longitudinal single-arm, and comparative prospective or retrospective cohorts, published between 2013 and 2018.[6-10]

Country of Origin

The studies were conducted in France,[6] Greece,[8] Portugal,[7] Russia,[7] Slovenia,[7] Italy,[9] and Hungary.[10]

Patient Population

All studies included adult patients with rheumatoid arthritis, most of whom were female, with a mean age ranging from 51.1[6] to 62.1[9] years.

Boleto et al.[6] recruited 134 patients from three rheumatology departments at university hospitals in France. Patients who met the American College of Rheumatology (ACR) 1987 and/or European League Against Rheumatism (EULAR) 2010 rheumatoid arthritis criteria and who were exposed to rituximab for at least 30 months were included. The sample population had a mean age of 52.1 years and 84.3% were female.

Chatzidionysiou et al.[7] used an anonymized dataset of patients who were diagnosed with rheumatoid arthritis and started treatment with rituximab. A total of 800 patients who had received at least one rituximab retreatment (i.e. two courses) and for whom information about retreatment strategy was available, were included in the study. At the second cycle of rituximab (i.e. first retreatment), 570 patients were included, and at the third cycle (i.e. second retreatment), there were 230 patients. The mean ages of the fixed interval and on-flare treatment groups were 51.1 and 49.5 years, respectively, for patients who received first retreatment, and 51.3 and 50.3 years old, respectively, for the patients who received second retreatment. Female participants comprised 87.4% of the sample.

The study by Vassilopoulos et al.[8] included 234 patients with moderate to severe rheumatoid arthritis (mean age: 59.0 years) across 17 academic and non-academic rheumatology hospital sites in Greece. The majority of patients were female (79.5%).

Quartuccio et al.[9] enrolled 102 unselected patients with longstanding rheumatoid arthritis who had an inadequate response to conventional DMARDs. The mean age of the patient population was 62.1 years and 88.2% were female.

The study by Vansca et al.[10] and included 77 patients with moderate or severe rheumatoid arthritis who had received one treatment of rituximab. The mean age was 52.8 years and 84.4% were female.

Interventions and Comparators

Initial rituximab treatment cycle

An initial treatment cycle of two doses of 1,000 milligrams (mg) rituximab, two weeks apart, was administered in all included studies,[7-10] with the exception of Boleto et al.,[6] which used two doses of 500 mg as an alternative.

Subsequent rituximab treatment cycles

Boleto et al.[6] examined a single routine 500 mg or 1,000 mg dose, with the time to retreatment determined by the physician and based on clinical response.

Chatzidionysiou et al.[7] examined fixed interval rituximab retreatment consisting of two courses (dose not provided) up to a total of three cycles, with the time period defined by the treating physician and varying among patients.

In Vassilopoulos et al.,[8] the retreatment schedule was two 1,000 mg doses, two weeks apart, repeated every six to 12 months, up to a total of seven cycles. The retreatment in Quartuccio et al.[9] was also two 1,000 mg doses, two weeks apart, administered at Month 6, although subsequent courses were provided every six months only if DAS28 <3.2 was not achieved. In Vancsa et al.,[10] the retreatment schedule was two 1,000 mg doses, two weeks apart, every six months regardless of clinical response, with at least five cycles administered within 24 months.

Comparators

Three studies had no comparator group.[6,8,10] Chatzidionysiou et al.[7] and Quartuccio et al.[9] compared fixed rituximab retreatment with as needed retreatment (i.e. based on flare).

Outcomes

Three studies[7,9,10] reported on efficacy outcomes and three studies[6,8,10] on safety outcomes. Two of the five studies evaluated safety only.[6,8]

Efficacy outcomes that were assessed by the included studies were the DAS28,[7,9,10] the HAQ,[9] and the European League Against Rheumatism (EULAR) response.[10]

The DAS28 is a measure of rheumatoid arthritis disease activity based on 28 joints, and assessment of swelling, tenderness, ESR or C-reactive protein (CRP), and global assessment of health on a visual analogue scale.[11] The overall disease score is based on a mathematical formula. A score greater than 5.1 indicates active disease, less than 3.2 is low disease activity, and less than 2.6 is remission.[11] The EULAR response classifies responses as good, moderate, or none based on improvement in DAS28 from baseline and the DAS28 score reached.[12] A good EULAR response is defined as improvement greater than 1.2 and endpoint score less than or equal to 3.2; a moderate response is improvement of greater than 0.6 to less than or equal to 1.2 and endpoint score greater than 3.2 to less than or equal to 5.1; and no response as improvement less than or equal to 0.6 and endpoint score greater 5.1.[12] The HAQ is a self-reported measure of functional status and pain with a higher score indicating worse outcome.[13]

Safety outcomes included hypogammaglobulinemia (< 6 grams per litre [g/L], severe < 4 g/L),[6] adverse events,[8] and serious adverse events.[6,8] Specifically, Vassilopoulos et al.[8] reported on infusion-related reaction, infection and serious infection, malignancy, adverse events leading to withdrawal, and death.

Follow-up ranged from 6.5 to 79.5 months.

Additional detail regarding the included studies is provided in Appendix 2.

Summary of Critical Appraisal

The non-randomized studies that comprised the evidence base for this topic were of poor quality overall. One study had fewer than 100 patients[10] and three studies had no comparator group.[6,8,10] A large number of patients dropped out or discontinued treatment in the studies of Boleta et al. (37%) and Vassilopoulos et al. (43%).[6,8] In addition, the study by Vassilopolos et al. was industry-funded; the sponsor designed the study, collected, analyzed and interpreted results, and compiled the clinical study report, which may potentially increase the likelihood of reporting positive results in favour of treatment.[8]

Two studies had a comparator group with sample sizes of 102, and 800.[7,9] In the prospective cohort of Chatzidionysiou et al., an analysis of an industry-supported registry that contained data on a large number of patients (N = 800) across three countries was conducted.[7] Baseline differences were present between the fixed interval and on-flare retreatment groups, with higher DAS28 in the on-flare group and a higher percentage in the fixed interval group on concomitant DMARDs and lower percentage on corticosteroids. This suggests the potential for confounding by indication, with higher disease severity among patients in the on-flare group. The models were adjusted for concomitant corticosteroid and DMARD use. The retrospective cohort by Quartuccio et al. (N = 102) also had a comparator group, however no adjustments were made for confounders on the outcomes of DAS28 or HAQ.[9]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

What is the clinical effectiveness of rituximab maintenance therapy for the treatment and management of rheumatoid arthritis?

Comparative studies

Efficacy

In a study that compared fixed interval rituximab retreatment versus on-flare retreatment (N = 800) up to a total of three cycles, DAS28 improvement from the start of therapy was statistically greater for the fixed interval group after both first and second retreatments.[7] In mixed-effects models adjusted for concomitant corticosteroid and DMARD use, the DAS28 estimated marginal means were statistically lower for fixed interval compared with on-flare for both first and second retreatments.[7] However, a study that compared fixed rituximab retreatment at Month 6 with as needed retreatment (N = 102), found no statistical differences among groups in DAS28 or HAQ, after 24 months of follow-up.[9]

Single-arm studies

Efficacy

In a study that administered rituximab infusion 1000 mg two weeks apart every six months to 77 patients, regardless of clinical response, the DAS28 was statistically lower after 24 months compared with baseline.[10] The EULAR responses were as follows: good response (change in DAS28 >1.2): 83.8%, moderate response (change in DAS28 0.6-1.2): 12.9%, and no response (change in DAS28 <0.6): 3.3%.[10]

Safety

Among 134 patients administered a routine single dose of 500 mg or 1000 mg rituximab infusion, hypogammaglobulinemia (<6 g/L) occurred in 17% after a mean follow-up of 79.5 months.[6] No case of severe hypogammaglobinemia (<4 g/L) was observed.[6] Severe infection (i.e. an infection requiring hospitalization and/or intravenous antibiotics) occurred in 9.7% and malignancy in 4.5%.[6]

In patients administered rituximab retreatment every six to 12 months (N = 234) and followed for a median of 27.7 months, adverse events occurred in 47.2%, serious adverse events (i.e. events that were fatal, immediately life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, were medically significant, or

required intervention to prevent one of the above outcomes) in 10.7%, infusion-related reaction in 8.6%, infection in 37%, and death in 1.3%.[8] Serious infection, malignancy, and adverse events leading to withdrawal occurred at rates of 2.53, 0.46, and 2.99 per 100 patient-years, respectively.[8]

No serious adverse events or serious infection were observed after 24 months of follow-up in patients administered rituximab retreatment every 6 months (N = 77).[10]

Additional information is provided in Appendix 4.

Limitations

The evidence consisted entirely of non-randomized studies, the majority of which were single-arm. Several studies were limited in the reporting of population and intervention characteristics. For example, most studies did not specify whether patients had responded to an initial cycle of rituximab infusion prior to receiving maintenance therapy.[6-9] In some studies, the number of rituximab infusions or doses received were unclear.[6,7,9] Poor reporting of the intervention details makes it difficult to assess whether the studies are relevant to clinical practice. In the study by Chatzidionysiou et al.,[7] the fixed interval time period between retreatment doses was defined by the treating physician and, therefore, varied among patients. In Vassilopoulos et al.,[8] retreatment was provided at six to 12 months, however no exact time interval was provided. Furthermore, it was unclear if retreatment was routinely administered or on-demand.[8]

The applicability of the evidence to Canadian rheumatology practice settings is unclear because all studies were conducted in other countries (i.e. France, Greece, Italy, Russia, and Hungary). The study by Vancsa et al. was carried out at a single hospital site.[10] The majority of study participants were female (80% to 88%), however, this is likely reflective of the higher prevalence in those who are female.

Conclusions and Implications for Decision or Policy Making

Three single-arm and two non-randomized comparative studies were evaluated in this review. The studies were of overall poor quality and the applicability to Canadian practice settings is unclear as all studies were conducted in other countries. In the largest study of 800 patients, fixed interval rituximab retreatment was associated with greater reduction of DAS28 compared with on-flare retreatment, however these results must be interpreted with caution due to the potential for confounding by indication.

Two additional studies were identified that contained relevant data, however these studies were not formally included in the review because they were published as an abstract[14] and a journal letter.[15] Avgoustidis et al. conducted a single-arm study in 247 patients, 27 of whom received maintenance rituximab infusion of 1000 mg every six months.[14] After a median follow-up of 12 months, 85% (23/27) of patients remained in remission or had low disease activity. Teng et al. conducted an open-label pilot study in 48 patients to examine single, fixed 1,000 mg rituximab retreatment at 24 weeks compared with on-demand retreatment.[15] No statistically significant differences were observed between groups in DAS28 change, HAQ change, radiographic progression, ACR20, ACR50, ACR70, or EULAR response, after one year of follow-up. In addition, no statistical differences were observed in the incidence of adverse events (86% vs. 95%), serious adverse events (18% vs. 15%), infusion-related adverse events (14% vs. 30%), adverse events leading to

withdrawal (14% vs. 5%), or death (4% vs. 0%). This was a small study and may have been underpowered.

Based on the evidence identified in this review, the benefits and safety of rituximab maintenance therapy are unclear. Studies that compare rituximab maintenance therapy with flare-based retreatment or other maintenance therapies would help to reduce the uncertainty.

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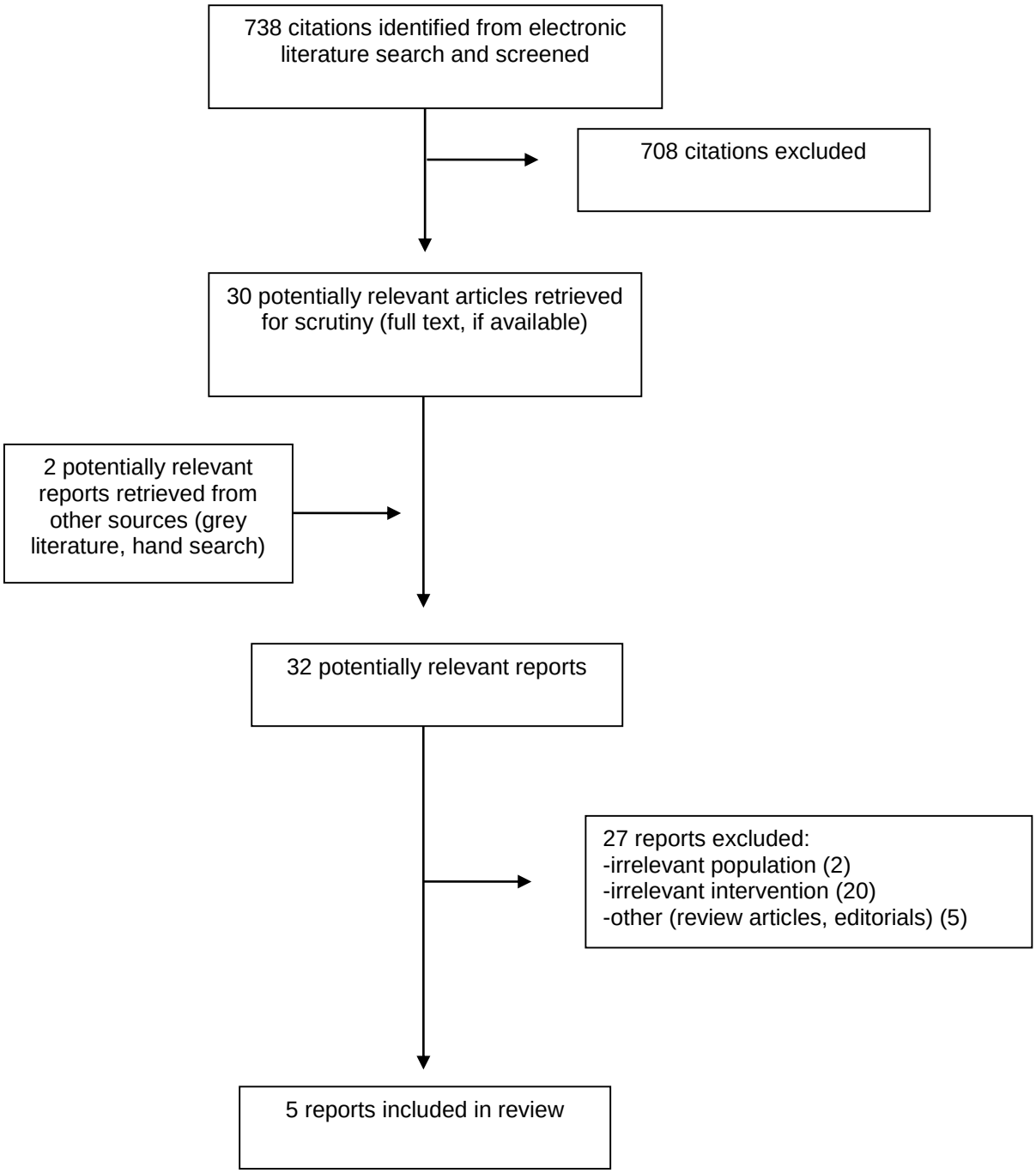
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Non-Randomized Studies

Author (Year)	Study Design & Location	Follow-up	Population	Intervention (I) & Comparator (C)	Outcomes
Boleto (2018)[6]	Longitudinal, single-arm France (3 rheumatology departments at university hospitals)	Mean ± SD: 79.5 ± 24.6 months	Met ACR 1987 and/or EULAR 2010 RA criteria Exposed to RTX at least 30 months N = 134 Mean age: 52.1 Female: 84.3%	RTX first infusion: 2 x 500 mg or 2 x 1000 mg, 2 weeks apart RTX retreatment: 500 mg or 1000 mg routine single dose; time to retreatment was determined by physician based on clinical response. Mean cumulative RTX dose ± SD: 12.0 ± 4.9 g **No comparator**	Hypogammaglobulinemia (<6 g/L, severe <4g/L) SAEs
Chatzidionysiou (2017)[7]	Prospective cohort CERERRA: Portugal, Russia, Slovenia (these countries had information on retreatment strategy)	Median months from RTX start: 1st retreatment (fixed interval & on-flare): 6.5 & 7.5 2nd retreatment (fixed interval & on-flare): 13 & 18.5	Received at least 1 RTX retreatment of 2 courses and for whom information about retreatment strategy was available. N = 800 N = 570 (1st retreatment) Mean age (fixed interval & on-flare): 51.1 & 49.5 N = 230 (2nd retreatment) Mean age (fixed interval & on-flare): 51.3 & 50.3 Female: 87.4%	RTX first infusion: 2 x 1000 mg, 2 weeks apart RTX retreatment (2 courses): fixed interval **Comparator:** RTX retreatment (2 courses): on-flare Up to a total of 3 cycles	DAS28
Vassilopoulos (2016)[8]	Longitudinal, single-arm	Median: 27.7 months	Patients with moderate to severe RA.	RTX first infusion: 2 x 1000 mg, 2 weeks apart	AEs and SAEs

Author (Year)	Study Design & Location	Follow-up	Population	Intervention (I) & Comparator (C)	Outcomes
	LAUNCH: Greece (17 rheumatology academic and non-academic hospital sites)		N = 234 Mean age: 59.0 Female: 79.5%	RTX retreatment: 2 x 1000 mg, 2 weeks apart; repeated every 6-12 months Up to a total of 7 cycles **No comparator**	Infusion-related reaction Infection and Serious infection Malignancy AE leading to withdrawal Death
Quartuccio (2015)[9]	Retrospective Cohort Italy (3 academic hospitals)	Data collected at month 12 in all patients and at month 24 in 55.9%.	Unselected patients with longstanding RA who had an inadequate response to DMARDs N = 102 Mean age: 62.1 Female: 88.2%	RTX first infusion: 2 x 1000 mg, 2 weeks apart RTX retreatment: Fixed: 2 x 1000 mg, 2 weeks apart, at Month 6 and subsequent courses every 6 months if DAS28 <3.2 was not achieved. **Comparator:** RTX retreatment**:** As needed 2 x 1000 mg, 2 weeks apart	DAS28 HAQ
Vancsa (2013)[10]	Longitudinal, single-arm Hungary (single center, university hospital)	24 months	Patients with moderate or high RA activity who had undergone one RTX treatment N = 77 Mean age: 52.8 Female: 84.4%	RTX first infusion: 2 x 1000 mg, 2 weeks apart RTX retreatment: 2 x 1000 mg, 2 weeks apart every 6 months regardless of clinical response At least 5 cycles in 24 months **No comparator**	DAS28 EULAR SAE Serious infection

ACPA = anticitrullinated protein antibodies; ACR = American College of Rheumatology; AE = adverse event; CERERRA = The European Collaborative Registries for the Evaluation of RTX in Rheumatoid Arthritis; DAS28 = Disease Activity Score, 28 joints; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; IgM = anti-immunoglobulin M; LAUNCH = Non-Interventional Safety Study of Rituximab in Patients with Severe Active Rheumatoid Arthritis; RA = rheumatoid arthritis; RF = rheumatoid factor; RTX = rituximab; SAE = serious adverse event; SD = standard deviation

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Non-Randomized Studies Using Downs and Black[5]

Strengths	Limitations
Boleto (2018)[6]	
• Long follow-up duration (79.5 months). • Outcomes were clearly defined.	• Study does not indicate whether patients responded to initial RTX treatment cycle before undergoing retreatment cycles. • No relevant comparator group. • Number of RTX infusions received is unclear. • Large number of drop-outs (36.6%) and characteristics of patients lost to follow-up not described. • Handling of missing data unclear.
Chatzidionysiou (2017)[7]	
• A comparator group was available. • Large sample size (N = 800) and multiple treatment centers. • The first retreatment mixed-effects model was adjusted for concomitant corticosteroids and DMARDs.	• Study does not indicate whether patients responded to initial RTX treatment cycle before undergoing retreatment. • The retreatment doses are unclear. • Fixed interval retreatment was defined by the treating physician; therefore, the fixed interval time period varied among patients. • Data on safety endpoints were not collected. • Baseline differences present between fixed interval and on-flare retreatment groups (e.g. slightly higher, but statistically significant, baseline DAS28 in on-flare group; higher percentage in fixed interval group on concomitant DMARDs and lower percentage on corticosteroids, compared with on-flare group). • The characteristics of patients lost to follow-up not described • The study results come from an industry-supported registry.
Vassilopoulos (2016)[8]	
• Subgroup analysis conducted for patients younger and older than 65 years. • Only one patient was excluded from analyses due to a protocol violation.	• Study does not indicate whether patients responded to initial RTX treatment cycle before undergoing retreatment. • Retreatment was provided at 6-12 months, however exact time interval not provided. Also, unclear if retreatment was on-demand or routinely administered. • No comparator group. • Large number of patients discontinued treatment (43.2%). • The study was industry-funded. The sponsor designed the study, collected, analyzed, interpreted, and wrote the clinical study report.
Quartuccio (2015)[9]	
• A comparator group was available. • Patients were enrolled into the study consecutively.	• Study does not indicate whether patients responded to initial RTX treatment cycle before undergoing retreatment. • Number of RTX cycles administered not provided. • Baseline differences present between fixed and as needed retreatment groups (e.g. slightly higher, but statistically significant, baseline DAS28 in as needed group; higher

Strengths	Limitations
	baseline HAQ in fixed retreatment group). • Effect estimates for DAS28 and HAQ were not adjusted for confounders. • At Month 24, only 55.9% of patients had clinical data, with larger number of drop-outs in the fixed retreatment group than as needed (fixed: 15/55 and as needed: 42/47).
Vancsa (2013)[10]	
• Long follow-up (24 months) • Dosing regimens and intervals were clearly reported.	• Patients were recruited from one department at a hospital in Hungary, which limits the generalizability of the results. • No comparator group. • Small sample size (N = 77). • Definitions of SAE and serious infections not provided.

DAS28 = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; RTX = rituximab; SAE = serious adverse event

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Boleto (2018)[6]	
Hypogammaglobulinemia: • <6 g/L: 23/134 (17.2%); 2.7 events per 100 pt-yrs • <4 g/L: no case **SAE:** • Severe infection: 9.7%; 1.5 events per 100 pt-yrs • Malignancy: 6/134 (4.5%); 0.7 events per 100 pt-yrs	"Repeated RTX [rituximab] courses and high cumulative doses were well tolerated with no additional safety concerns following further exposure." (p.5)
Chatzidionysiou (2017)[7]	
DAS28 improvement from RTX start: 1st retreatment (mean ± SD): • Fixed interval: -1.9 ± 1.5 • On-flare: -1.0 ±1.9 p<0.0001 2nd retreatment (mean ± SD): • Fixed interval: -1.9 ± 1.5 • On-flare: -1.0 ±1.9 p<0.0001 **DAS28 estimated marginal means (adjusted mixed model):** 1st retreatment – mean (95% CI): • Fixed interval: 3.8 (3.6, 4.1) • On-flare: 4.6 (4.5, 4.7) p<0.0001 2nd retreatment – mean (95% CI): • Fixed interval: 3.7 (3.3, 4.0) • On-flare: 4.6 (4.4, 4.8) p<0.0001	"The results of the mixed-model regression analysis suggested that a fixed retreatment approach, before a flare occurs, might lead to more favorable results." (p.168)
Vassilopoulos (2016)[8]	
AEs: 110/233 (47.2%); 48.36/100 pt-yrs (95% CI: 42.04, 55.36) **SAEs:** 25/233 (10.7%); 6.68/100 pt-yrs (4.47, 9.59) **Infusion related reaction:** 20/233 (8.6%); 4.61/100 pt-yrs (2.81, 7.11) **Infection:** 77/210 (37%); 17.73/100 pt-yrs (13.99, 22.16) **Serious infection:** 2.53/100 pt-yrs (1.26, 4.53) **Malignancy:** 0.46/100 pt-yrs (0.06, 1.66) **AE leading to withdrawal:** 2.99/100 pt-yrs (1.59, 5.12) **Death:** 3/233 (1.3%); 0.69/100 pt-yrs (0.14, 2.02)	"The percentage of patients that experienced any AEs [adverse events] was higher during the first two cycles (cycle 1: 21%, cycle 2: 19.5%) and decreased over the subsequent cycles . . . The same pattern was observed regarding the SAEs [serious adverse events] and infections throughout the cycles" (p.898) "The safety profile of RTX [rituximab] was compared between patients younger or older of 65 years of age . . .In general, patients older than 65, had a statistically significant higher incidence rate of AEs and SAEs compared to younger patients (Incidence rate ratios: 1.53, 95% CI: 1.16-2.02, p=0.002 and 2.88, 95% CI: 1.34-6.21, p=0.005, respectively). Although, infections and SIEs [serious infections] were also more common in older patients the difference was not statistically significant . . ." (p.898)

Main Study Findings	Author's Conclusion
Quartuccio (2015)[9]	
DAS28: • **Month 12: median (range)** Fixed: 4.0 (2.3 - 7.1) As needed: 4.1 (1.7 – 7.7) p = 0.86 • **Month 24: median (range)** Fixed: 3.3 (2.3 - 7.0) As needed: 3.4 (1.4 – 7.6) p = 0.91 **HAQ:** • **Month 12: median (range)** Fixed: 1.8 (0 – 3.0) As needed: 1.2 (0.1 – 3.0) p = 0.0004 • **Month 24: median (range)** Fixed: 1.7 (0.1 – 2.3) As needed: 1.2 (0.1 – 3.0) p = 0.37	"The analyses demonstrated that a treatment as needed regimen is cost effective when compared with a fixed 6-month retreatment regimen in longterm timeframe scenarios. Caution is needed to generalize this result, and the choice of the RTX [rituximab] retreatment regimen should take into account the level of disability and the placement of RTX in the treatment strategy in the single patient. . ." (p.954)
Vancsa (2013)[10]	
DAS28: • Baseline: mean (SD) 5.36 (0.34) • 24 months: mean (SD) 3.43 (0.31) p < 0.001 **EULAR (24 months):** • Change DAS28 >1.2 (good response): 83.8% • Change DAS28 0.6-1.2 (moderate response): 12.9% • Change DAS28 <0.6 (no response): 3.3% **SAE:** none **Serious infection:** none	"The fixed treatment protocol may result in overtreatment of patients. However, because no serious adverse events were observed, this may not be an issue." (p.570)

AE = adverse event; CI = confidence interval; DAS28 = Disease Activity Score; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; IQR = interquartile range; pt-yrs = patient-years; RTX = rituximab; SAE = serious adverse event; SD = standard deviation

Appendix 5: Additional References of Potential Interest

Emery P, Mease PJ, Rubbert-Roth A, et al. Retreatment with rituximab based on a treatment-to-target approach provides better disease control than treatment as needed in patients with rheumatoid arthritis: a retrospective pooled analysis. Rheumatology (Oxford, England). 2011;50(12):2223-2232.
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Mease PJ, Cohen S, Gaylis NB, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. J Rheumatol. 2010;37(5):917-927.
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