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Lessons For Rituximab Therapy In Patients With Rheumatoid Arthritis – 15 years of experience

Leticia Garcia-Montoya[1,2], Catalina Villota-Eraso[3], Md Yuzaiful Md Yusof[1,2], Edward M Vital[1,2], Paul Emery[1,2]

1 Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK
2 NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
3 Hospital Universitario San Ignacio, Bogotá, Colombia

ABSTRACT

B-cell depletion therapy is an effective option for RA treatment, but depletion is frequently incomplete (>0.0001x10^9/L at week 2). Complete B-cell depletion (CD) after rituximab is associated with good clinical response (R) and this status (CD-R) leads to long-term maintenance of therapy. Low pre-treatment plasmablasts, concomitant DMARDs, no smoking exposure, ACPA/RF+ and a low IFN-signature are predictive of CD-R. Half of the patients that achieve CD-R with rituximab eventually stop experiencing this outcome to further infusions; however 3/4 of them regain it in the following cycle. This suggests that loss of response is reversible and patients can still benefit from rituximab re-treatment. Efficacy of lower doses of rituximab is under investigation, but preliminary results suggest these strategies are best used for maintenance especially in patients who suffer adverse events or are at high risk of infection. Infusion reactions are the most common adverse events; and IgG monitoring is crucial as low levels correlate with higher infection risk.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterised by joint inflammation, stiffness and involvement of tendons and ligaments. If untreated, it leads to disability and irreversible joint destruction. It can appear at any age, but it is more commonly diagnosed in patients between the age of 40 and 60 years old. The estimated prevalence in the UK is around 1% of the population, with 15% having severe disease (1).

Despite major advances, the pathological mechanisms underlying RA are not fully understood; treatments are based on the inhibition of specific molecular or cellular targets known to be involved in the disease, such as B-cells. Rituximab is a chimeric monoclonal antibody that depletes these cells by binding to the CD20 molecule on their surface (figure 1). Its efficacy and safety have been demonstrated in several trials (2-6) ; however, treatment can (and should) be individualized if predictive factors for treatment response are identified. In this paper, we will focus on the lessons learnt in the last two decades from treating RA with rituximab (over 1000 patients in a single centre in the UK).

SEARCH STRATEGY AND SELECTION CRITERIA

An electronic search was carried out in PubMed, MEDLINE, Embase, Cochrane Library, ACR and EULAR abstract archive from 1996 to August 2019. The search was performed using two themes combined by the Boolean operator "AND". For the theme "rituximab", the following words were used: "rituximab", "anti-CD20", "B-cell depletion", "Mabthera", "Rituxan", "Truxima", "CT-P10", "Ruxience", "PF-05280586", "Rixathon", "GP2013". For the second theme, "rheumatoid arthritis", the following words were used: "rheumatoid", "RA" and "arthritis". Only articles published in English language were selected. The references cited were chosen based on their relevance to the contents of this paper.

THEORETICAL BASIS FOR B-CELL DEPLETION

For many years, T-cells were considered to be the main cell responsible for RA pathology (7). However, the identification of auto antibodies in RA implied that a humoral immune disorder was also present in the disease; which lead to a revival of interest in the role of B-cells (7,8).

B-cells are a recognized component of the adaptive immunity; however, they also act as a bridge between innate and adaptive immune systems (7). In RA, autoreactive B-cells are not eliminated before becoming mature; resulting in plasma cells producing autoantibodies such as anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF). These autoantibodies represent a break in tolerance and are also markers of severe disease (9).

Activated autoreactive B-cells exist in the synovium and circulate in peripheral blood. Not only are they antibody producers, but they can also act as antigen presenting cells to T-cells, leading to T-cell mediated inflammation (7). Moreover, B-cells are also prolific producers of inflammatory cytokines such as tumour necrosis factor (TNF) α, IL-6, IL-12, IL-23 and IL-17(10).

Rituximab targets B-lymphocytes by binding to CD20 surface antigen; which leads to B-cell depletion via complement-dependent cell lysis, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and apoptosis (11)(figure 1). Nevertheless, 5% of the B-cell lineage do not express CD20 on their surface: these are stem cells, pro-B-cells, terminally differentiated plasma cells and plasmablasts. The fact that hematopoietic precursors are not affected, permits re-treatment by allowing B-cell regeneration and a continued production of immunoglobulins from plasma cells; particularly from the long-lived subtype (12).

WHEN TO USE RITUXIMAB

The goal of treat-to-target (T2T) strategy in RA is to achieve clinical remission or low disease activity: this results in decreasing joint pain and swelling, halting radiographic progression and preserving a good quality of life (13). Therapy involves the use of disease-modifying anti-rheumatic drugs (DMARDs), and can require non-steroidal anti-inflammatories (NSAIDs) and corticosteroids for short-term management (1). Conventional synthetic DMARDs (csDMARDs) are considered the first line therapy for newly diagnosed RA, with methotrexate (MTX) used as the cornerstone of treatment (13). Most guidelines, including those from EULAR, suggest adding a biologic DMARD (bDMARD) or a second targeted csDMARD in combination with MTX in the following situations: a) if a significant improvement is not achieved within 3 months, b) if remission/low disease activity is not achieved within 6 months since treatment initiation (13). However, in some countries such as the UK and Canada, rheumatologists are required to use at least two csDMARDs before initiation of a bDMARD (13).

bDMARDs have comparable efficacy regardless of their target. If one of them fails, commencing another bDMARD, preferably with a different mode of action, is standard practice (13).

Rituximab is indicated for patients with severe active RA who have an inadequate response or intolerance to one or more TNFis (14); however, it is also used as first bDMARD in patients with contraindication to these drugs. Rituximab has demonstrated its efficacy against placebo in biologic naïve RA patients in the SERENE trial (4) as well as its non-inferiority to TNFi in the ORBIT open-label trial (15).

Interstitial lung disease (ILD) is a significant pulmonary morbidity associated with RA. Previous reports studies have shown adverse events and worsening of ILD from the use of TNFis (16). In contrast, the use of rituximab has shown stability of lung function and symptoms over a prolonged period of time and is commonly used when this lung disease is present (17).

ADMINISTRATION AND EFFICACY

Rituximab is licensed for the treatment of RA at a dose of 2 intravenous (IV) infusions of 1,000 mg each on the days 1 and 15, and it is usually preceded by a dose of IV glucocorticoids (most frequently 100mg of methylprednisolone) right before each infusion (14). Even though DANCER study showed that neither this nor the addition of following oral steroids make a significant improvement to the efficacy of the drug, IV glucocorticoids are requited by NICE guidelines as they reduce the incidence of acute infusion reactions, especially with the first rituximab infusion (2). Alternatively, *Carter el at.* (18) suggested that a smaller dose of oral prednisone may be as efficacious and well tolerated, and could decrease the administration time.

Several possible rituximab/DMARD combinations have been assessed (including leflunomide), showing apparent efficacy (14). Nevertheless, combination with MTX is the most highly encouraged as the 2016 EULAR recommendations (13) state that all bDMARDs, including rituximab, have a superior efficacy in combination with MTX. This regime is associated with improvements in physical function and reduction of RA symptoms for longer than 1 year compared with rituximab monotherapy (6) .

Reduced doses

There has been controversy regarding the use of reduced doses of rituximab. Whereas most trials indicate that reduced doses have a similar efficacy (19), a few studies have reported a slightly increased benefit with the standard dose of rituximab (2-4, 20-22) (table 1).

DANCER, a phase IIB randomized, double-blind, placebo-controlled trial (2) compared three regimes in inadequate responders to MTX or TNFis: 1) a standard full dose of two 1000mg infusions of rituximab separated by two weeks, 2) a lower dose of two 500mg infusions separated by two weeks and 3) rituximab placebo; all of these in combination with MTX. It was confirmed that both doses of rituximab were effective, safe and well tolerated over 24 weeks; however, the stringent ACR70 response was higher in patients receiving the standard dose of rituximab.

Supporting these observations, the MIRROR trial (3) analysed the efficacy of three rituximab regimes in the same population, consisting on two cycles separated by 24 weeks: 1) two 2x500mg infusions; 2) dose escalation of one cycle of 2x500mg followed by one cycle of 2x1000mg; 3) two cycles of 2x1000mg. It was showed that patients treated with rituximab 2x1000mg had higher response and maintenance rates.

In contrast, SERENE trial (4), a double-blind, randomised, placebo-controlled phase III study compared response rates in three groups of patients of inadequate responders to MTX: one receiving 2x500mg of rituximab, another group receiving 2x1000mg and a third group receiving placebo; all of these combined with MTX. Although rituximab was efficacious compared to placebo, there were no significant clinical differences between the two rituximab groups.

The IMAGE study (20), a similarly designed double-blind, randomised, placebo-controlled phase III trial, compared the same treatment regime as SERENE trial, but in a MTX naïve population. This trial evaluated radiographic progression. Whereas both rituximab regimes seemed to have equal clinical efficacy, only the 1000mg rituximab dose significantly reduced the progression of joint damage. The extension of this study to 2 years showed that after this point, radiographic progression was minimal, however all radiographic end points assessed from enrolment up to 2 years were better for the standard rituximab dose (21).

Additionally, non-inferiority studies have also been undertaken. *Mariette et al.* (22) compared the efficacy and safety of retreatment with 1000mg of rituximab vs 2x1000mg in RA patients who had previously received a standard full dose and had achieved clinical response. Efficacy was maintained in the lower dose retreatment arm with no significant differences in safety compared with the licensed doses.

Data from observational cohorts such as CERERRA collaboration support that a lower dosage of rituximab leads to comparable clinical outcomes at 6 months (23). In addition, another five year follow-up observational cohort also reported a decreased risk of serious infections that may be linked to a better maintenance of IgG levels (24).

Other potential benefits of reduced rituximab doses are a shorter time of infusion administration, together with a lower incidence of first infusion reactions (19). Furthermore, lower-dose regimes could be an important strategy to reduce expenses as they seem to be more cost effective: the results of a meta-analysis (19) showed that 20 patients would have to be treated with standard dose of rituximab for one patient to achieve remission. This would imply an additional cost of € 4000/patient/year (assuming a mean interval of 9 months between cycles).

Considering that most trials only offer only short term data, for real-life practice we would advise physicians to follow Marriette's approach and only use a low rituximab dosage (usually 2x 500mg) in stable patients that have previously received induction with a standard rituximab regime (22).

EVIDENCE FOR AIMING FOR COMPLETE B CELL DEPLETION

a) Overview

An initial study by *Breedveld et al*. (25) found no correlation between clinical response to rituximab and B-cell numbers. These results could be explained by the fact that blood samples were analysed using conventional flow cytometry [Fluorescence-activated cell sorting (FACS)]. This technique can detect a number of B-cells of $0.005x10^9$ cells/litre. In contrast, highly sensitive flow cytometry (hsFACS), a technique that was initially used by haematology to detect minimal residual disease in malignancies, is able to detect counts as low as 2-log lower numbers; which considerably increases the sensitivity.

Using hsFACS, *Dass et al*. (26) demonstrated that incomplete B-cell depletion after rituximab therapy was associated with a poorer outcome. Also, preliminary results seem to support that in patients with initial response to rituximab, early depth of B-cell depletion is associated with long maintenance of

therapy (27). Unfortunately, once rituximab is administered, not all patients will achieve complete depletion. Should this be the case, one approach showed that an additional 1000mg of rituximab at 4 weeks enhanced B-cell depletion and better response rates compared to placebo (28).

b) Predictors of complete B-cell depletion and response

Plasmablasts are the immature precursors of plasma cells. They are CD20 negative but are replenished by CD20 positive B-cells which makes them a potential biomarker for B-cell depletion after rituximab therapy (29). Studies have reported that a low number of plasmablasts before rituximab infusion increases the odds ratio for complete B-cell depletion with clinical response (CD-R) . As *Vital et al*. suggested, response to treatment seems to be determined by the degree of B-cell depletion and not by the dose of rituximab (30); and in case of incomplete depletion, most of these remaining B-cells are plasmablasts. In addition to this, other studies highlighted the importance of memory B-cells; whose high levels before treatment are associated with poor response to rituximab and early relapse (31).

The auto-antibody status also seems to play a role in this predictive model, as seropositive patients achieve a better EULAR response with rituximab (32). *Thurlings et al*. reported that in good responders, reduction in ACPA levels correlated with a decrease in plasma cells (33). However, after an initial fall, the ACPA titre stabilised (34). In contrast, *Quartuccio et al*. (35) stated that it was RF positivity and not ACPA positivity that is associated with better EULAR responses.

In terms of histology, data have shown that the levels of synovial B-cells after rituximab do not necessarily correlate with the peripheral blood levels (36). One study performed a synovial biopsy before, 4 and 16 weeks after the administration of rituximab; even though there were not baseline biomarkers predictive of response, there was an association between decrease of plasma cells in the synovial tissue and clinical response at 6 months (33).

Type I Interferon (IFN-I) is linked to B-cells as it can stimulate plasma cell differentiation and it is involved in early B-cell activation (37). Results show that a high IFN signature is associated with poor response to rituximab (38). Some of the possible explanations that have been suggested are that type I IFNs could favour the survival of pathological B-cells in the lymphoid organs (39); that high IFN activity might be linked to a B-cell subtype insensitive to the effects of rituximab (perhaps due to larger numbers of plasmablasts with a greater B-cell drive to be overcome) (40); and less likely, that the pathogenesis of high IFN patients might be less dependent on B-cells compared with the low signature subjects (41).

Regarding other epidemiological factors, the effect of smoking is controversial: whereas some studies found that smoking is not an important predictor for response (42), many others show that patients who have never smoked have higher response rates (27, 43). Among active smokers, ACPA or RF positive individuals seem to be more likely to respond (43); but regardless of the antibody status, smoking cessation is advised for better treatment outcomes.

T-cells play an important role in the pathogenesis of RA, and are also affected by rituximab therapy. *Stradner et al*. (44) suggested the combination of plasmablasts with the lymphocyte count, T-cells and CD4+ T-cells in order to predict treatment response. Furthermore, several articles have confirmed a decrease in CD4+ T-cells following rituximab administration in RA patients showing clinical response (45). This decrease fully recovers at the end of every rituximab cycle and seems to occur at the time of disease relapse. This contrasts with B-cells; which may not have fully recovered by the time the following rituximab infusion is administered, and are more likely to be decreased with consecutive cycles (46).

Finally, an abstract (27) showed that the combination of DMARDs with rituximab is associated with achieving higher rates of B-cell depletion and response. This would explain the better outcomes of this combined therapy compared with rituximab alone.

c) Is reconstitution related to a flare of the disease?

Between 5 to 12 months after treatment, B-cells depleted by rituximab return to the circulation and with this, disease activity may return (47). Studies suggest that it is possible to predict disease relapse by monitoring the repopulation of B-cells (48). This would allow physicians to personalise the retreatment strategy and reduce the number of adverse events.

MAINTENANCE THERAPY

Results from a rituximab cohort containing over 600 patients showed that early complete B-cell depletion was associated with longer maintenance of therapy (27).

Studies support that a fixed re-treatment strategy has a clear benefit over receiving rituximab after flaring and patients on the former regime tend to have lower disease activity. The DAS28 decreases at the same time as remission rates improve with repeated cycles (49). Therefore, we believe that subjects who are most likely to benefit from fixed strategies are those who have continued disease activity, and do not achieve clinical remission (14).

Considering that treatment at a fixed interval implies receiving more rituximab cycles, there is a concern that some patients may develop hypogammaglobulinemia; which is associated with an increased risk of serious infections (50,51). Even though patients on a fixed re-treatment strategy may present a higher number of infections, the safety profiles of these two strategies seem to be comparable (52).

Finally, one of the main concerns regarding a fixed re-treatment strategy is the elevated drug cost. As described above, the use of lower dosage could be a solution for this as not only it did not affect the maintenance of therapy after 5 years, but also had the advantage of fewer serious infections (24).

LOSS OF RESPONSE TO RITUXIMAB

Early depth of B-cell depletion with clinical response leads to a better long-term outcome (27) but unfortunately, at some point almost half of the patients lose CD-R with subsequent cycles (53). An observational study (53) with over 700 patients treated with rituximab showed that 84% of those who lost CD-R can regained it with further treatment, with 77% of them doing so in the following cycle. Interestingly, 33% of patients that either lost clinical response or did not achieve complete B-cell depletion, never received further treatment with the drug and were switched to other therapies. Some physicians may do this following a treat-to-target principle, in which switching of treatment is indicated in case of loss of response. Nevertheless, data suggest that unlike continuous treatment with TNFis, the loss of this optimal status with an intermittent drug like rituximab is reversible, and patients can potentially experience improvement again. This is an important message for physicians so that a valuable therapy is not discarded.

ADVERSE EVENTS

The long-term safety data of RA patients treated with repeat cycles of rituximab combined with MTX have been pooled from eight randomised controlled trials (RCT) and two long-term extension (LTE) studies; with a total follow-up of 11,962 patient-years (50) (table 2).

Infusion reactions

Infusion reactions are characterized by nausea, headache, hypotension, pruritus, urticaria and flushing within the first 24hours post-infusion. They are the most common adverse events; occurring in a quarter of patients receiving the first drug administration. The frequency of these events rapidly decreases with the second rituximab infusion and pre-medication (6). The underlying mechanism is related to complement and cytokine activation and they appear more frequently in patients with hematologic malignancies than in those who receive rituximab for the treatment of autoimmune diseases (54). The management of acute infusion reactions consists of stopping the rituximab infusion plus paracetamol, diphenhydramine (which are usually given as premedication) and IV steroids (55).

Serum sickness

Serum sickness is a rare severe adverse event mediated by immune complexes. Clinical presentation includes fever, gastrointestinal symptoms, rash, lymphadenopathy, proteinuria, haematuria, and arthralgia. It usually appears from 8 to 13 days after the first rituximab infusion or a few days following rituximab re-treatment (56), and more commonly in patients with overlapping conditions such as hypergammaglobulinemia in addition to RA (57). HACA antibodies are associated with the most severe cases serum sickness disease, especially in repeat rituximab cycles (57). Treatment is corticosteroids, which are usually administered for a mean of 9 days and antihistamine can be used for mild symptoms (57).

Infections

In rituximab trials, 35% of individuals in the rituximab group suffered an infection of any type, in comparison with the 28% of those receiving placebo (2). The most common ones are upper respiratory tract infections, nasopharyngitis, urinary tract infections, bronchitis and sinusitis (5). Infections happen more frequently during the first 3 months after drug infusion (5). Severe infections have also been reported: these included bronchopneumonia, cellulitis, urinary tract infection, colitis and sepsis. Consecutive rituximab cycles do not seem to increase the infection rate and the incidence also appears to be similar in patients receiving concomitant DMARDs and those who are not. There are no differences either between those who receive prior treatment with systemic steroids and those who do not; however, the rate of infections is increased in those who receive them chronically (58). Less than 3% of RA patients develop neutropenia after rituximab infusion and only 1% of cases are severe (neutrophils $<0.5 \times 10^9/l$). Most of them have a quick recovery with no evidence of worsening with repeat cycles (59).

Opportunistic infections are rare (5,60).The incidence of tuberculosis remains low, with only two cases of pulmonary tuberculosis and no cases of extra-pulmonary or multi-drug resistant forms reported in the all-exposure population from RCT and LTE studies. Even though screening for latent tuberculosis is not mandatory, it is expected that this will have been done in patients previously exposed to TNFis (50,60).

Hepatitis B (HBV) reactivation is a risk in patients who are “HBsAg-positive” or “HBsAg-negative and HBcAb-positive”. Liver failure has been described, more often in patients with non-Hodgkin lymphoma treated with rituximab (61). Even though no cases of HBV reactivation have been reported in long-term safety trials for RA (50,60), a study found that 9% of RA patients who were HBsAg-/HBcAb+ had HBV reactivation (62). Hepatitis C (HCV) activation after rituximab has also been reported, but not described in detail (63). A study carried out in Taiwan with 26 RA patients that were not on any anti-viral therapy, compared the viral activity of those receiving rituximab vs TNFis. Whereas the latter did not seem to affect viral replication, the viral load was increased in patients receiving rituximab (64). Monitoring the viral load in patients with HCV is essential.

Immunoglobulin levels have been assessed in multiple rituximab trials. Whereas short term studies have reported maintained levels of IgM and IgG (2), long-term trials observed a decrease, particularly of IgM after rituximab treatment (50). Registry data shows that lower IgG levels before rituximab administration (<6 g/l) are associated with higher risk of serious infection events (SIEs)(65); furthermore, this increased risk was also present if low IgG levels developed during or after rituximab treatment. Some risk factors related to hypogammaglobulinemia are older age, chronic lung disease, and previous history of cancer (51). In all patients, but especially in these cases, immunoglobulin quantification should be done before and after each rituximab administration (14,51).

The development of progressive multifocal leukoencephalopathy (PML) has been reported in patients with rheumatic diseases but also in patients exposed to certain immunosuppressive therapies. From 2002 to 2015, nine cases of PML were confirmed in patients with RA with an estimated exposure of 351,396 patients. However, in spite of the increasing use of rituximab, the reporting rate of PML has continued to be stable and is a very rare event (66).

Cardiovascular

Even though the incidence of myocardial infarctions did not increase with rituximab, patients must be monitored throughout the drug infusion (60) and cardiovascular risk factors monitored as for all RA patients.

Malignancies

Some malignancies have been described after exposure to rituximab. The most commonly reported ones are skin neoplasms, and breast cancer (5,60). Nevertheless, similar rates are expected for RA population who previously received immunosuppressive therapies (67). Safety trials have demonstrated that malignancy risk is not increased during therapy with rituximab compared with non-biologic treatment (60,67,68).

SWITCHING TO OTHER BIOLOGICS

Current guidelines advise the use of rituximab after failure of TNFi treatment; however, if response to rituximab is lost, many patients are actually switched back to a TNFi. Even though safety is not compromised with this treatment (69), using a bDMARD with an alternative mode of action may be a preferable option: IL-6 plays a key role in RA as it is involved in T-cell differentiation and B-cell function (70). In patients who do not experience clinical response in spite of complete B-cell depletion, IL-6 levels are often elevated (71). Tocilizumab, a humanised monoclonal antibody that binds to the cell receptor of IL-6 seems to be a more effective treatment in these patients (71). Abatacept, a fusion protein formed by the extracellular domain of CTLA-4 and the Fc domain of human IgG1 is able to block T-cell co-stimulation; however its efficacy after rituximab seems to be lower than that of IL-6 blockade (71).

SWITCHING TO A BIOSIMILAR

Considering the cost of biologic therapies, there has been an increasing interest in the development of biosimilar drugs. The patent of rituximab ended in the European Union and the United States in 2015 and CT-P10 (Truxima) was the first rituximab biosimilar to be approved for the same indications and regime as the originator.

In a randomised phase I trial (72), CT-P10 demonstrated similar pharmacokinetics and comparable efficacy, pharmacodynamics, immunogenicity and safety to rituximab. Long-term efficacy was confirmed in a phase III multinational double-blind trial (73), showing no significant differences with Mabthera/Rituxan for the ACR20, ACR50, and ACR70 response rates at week 48.
In patients that initially received rituximab and switched to CT-P10, B-cell depletion rates, efficacy, safety, anti-drug antibodies and the number of infusion-related reactions remained similar to those who received CT-P10 from the beginning (74).

GP2013 (Rixathon) is the latest anti-CD20 biosimilar to be approved in the EU, Switzerland, Japan and Australia. It has also demonstrated similar pharmacokinetics, pharmacodynamics, immunogenicity, safety and efficacy to rituximab in a multinational, randomised, double-blind, parallel-group study (75); however it is not yet approved in the US.

CONCLUSION

Experience with Rituximab have shown it to be a safe and effective drug for the treatment of seropositive RA in patients that do not respond to TNFi therapy or in whom the latter is contraindicated. Studies demonstrate that CD-R is the optimal status as this is associated with longer maintenance on therapy. Individual assessments can be done in order to predict this response to rituximab; and even when lost, this status can be recovered with further cycles. Regarding the use of reduced doses, results are somewhat controversial; however, we believe they are an option in patients with comorbidities or in those at a high risk of infection. Optimisation of drug use represents a first step to improving the management of RA.

Conflicts of interest: LGM, CVE and MYMY have no conflicts of interest. EV reports personal fees from Roche and Genentech, personal fees from Becton Dickinson, outside the submitted work. PE reports grants and personal fees from BMS, AbbVie, MSD, Pfizer and Roche and personal fees from Novartis and UCB, outside the submitted work.

Contributors: LGM, CVE and PE substantially contributed to the conception and design of the work, the acquisition, analysis and interpretation of data, drafting the work and revising it critically for important intellectual content, final approval of the version published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MYMY and EV substantially contributed to the conception and design of the work, analysis and interpretation of data, drafting the work and revising it critically for important intellectual content and final approval of the version published.

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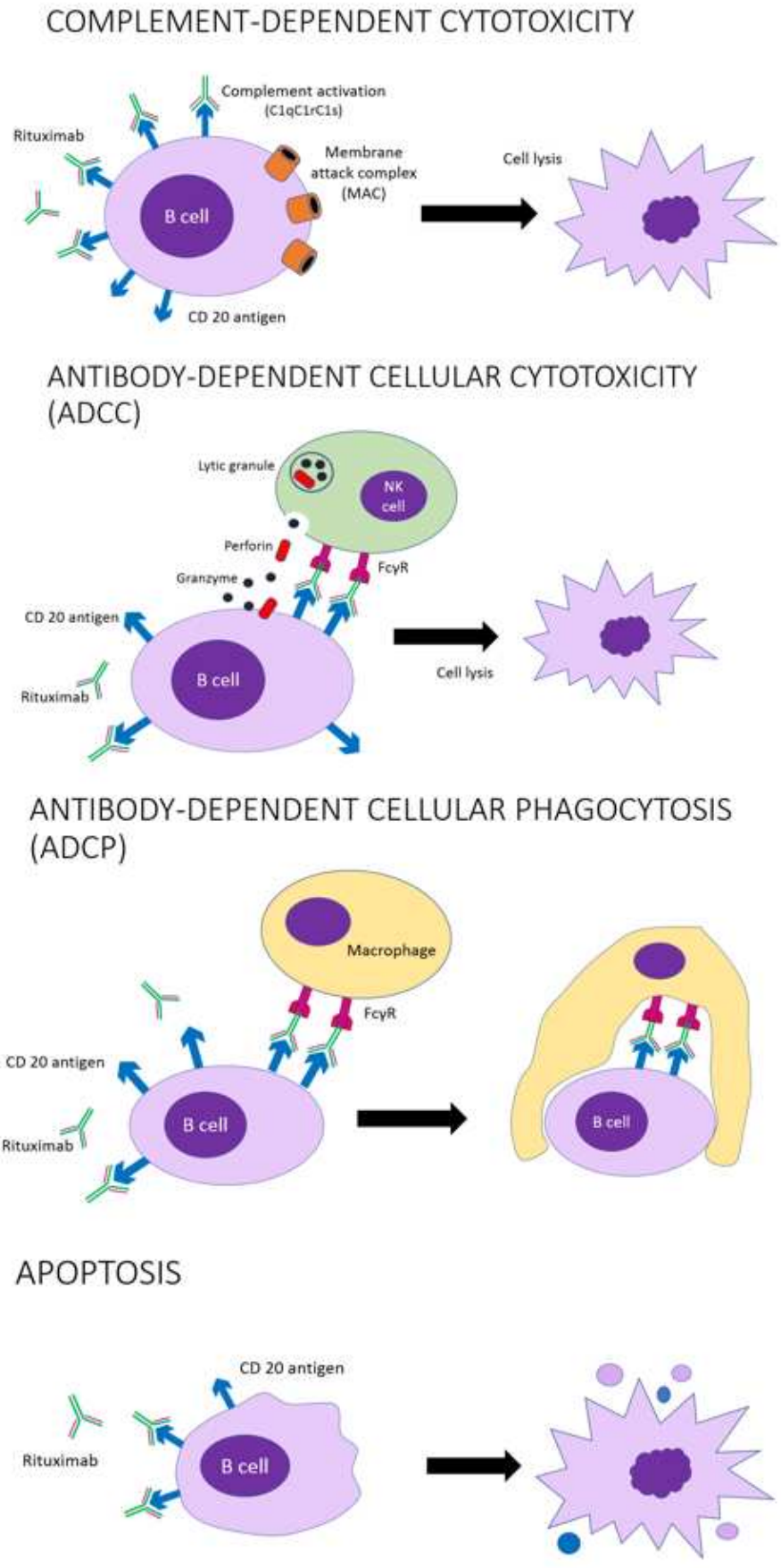

Figure 1. Rituximab mechanisms for B-cell depletion.

COMPLEMENT-DEPENDENT CYTOTOXICITY: Rituximab binds to the CD 20 antigen, and at the same time, complement binds to it activating the membrane attack complex on the B cell. This protein formation works as a channel that allows water and ion influx that results in lethal colloid-osmotic swelling.

ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC): FcγR receptors on Natural Killer (NK) cells can recognise the binding of rituximab to B cells and trigger degranulation and cell lysis.

ANTIBODY-DEPENDENT CELLULAR PHAGOCYTOSIS (ADCP): Once rituximab attaches to CD20 antigens, FcγR receptors on macrophages or other phagocytic cells, can bind to the antibodies and trigger phagocytosis.

APOPTOSIS: Rituximab binding to CD 20 antigen can lead to direct signalling of apoptosis.

YEAR	TRIAL	RANDOMISED PATIENTS (n)	PATIENT CHARACTERISTICS	TREATMENT ARMS	OUTCOME
2006	DANCER (P.Emery et al.)	465	Inadequate response to MTX or TNFis	1) MTX + RTX placebo + steroids placebo 2) MTX + RTX placebo + IV steroids 3) MTX + RTX placebo + IV steroids + PO steroids 4) MTX + 2x RTX 500mg + steroids placebo 5) MTX + 2x RTX 500mg + IV steroids 6) MTX + 2x RTX 500mg + IV steroids + PO steroids 7) MTX + 2x RTX 1000mg + steroids placebo 8) MTX + 2x RTX 1000mg + IV steroids 9) MTX + 2x RTX 1000mg + IV steroids + PO steroids	• Higher rates of ACR70 and EULAR good response in patients receiving 2x RTX 1000mg • Efficacy not influenced by steroids
2010	SERENE (P.Emery et al.)	511	Inadequate response to MTX	1) MTX + RTX placebo 2) MTX + 2x RTX 500mg 3) MTX + 2x RTX 1000mg	Both RTX doses have similar efficacy
2010	MIRROR (A. Rubbert-Roth et al.)	378	Inadequate response to MTX or TNFis	1) MTX + 2x (2x RTX placebo) 2) MTX + 2x RTX 500mg, dose escalation to MTX + 2x RTX 1000mg 3) MTX + 2x (2x RTX 1000mg)	2x RTX 1000mg dose (vs 2x 500mg) showed: • Higher rate of patients achieving remission • Higher rate of patients achieving EULAR good/moderate response • Higher rate of patients maintaining their week 24 ACR response
2011	IMAGE (P. Tak et al.)	755	MTX naïve	1) MTX + RTX placebo 2) MTX + 2x RTX 500mg 3) MTX + 2x RTX 1000mg	• Both RTX doses have similar response rates • Only the 2xRTX 1000mg dose significantly reduced progression of joint damage
2014	SMART (X.Mariette et al.)	100	Inadequate response to TNFis	MTX + 2x RTX 1000mg. 24weeks later: 1) RTX 1000mg 2) 2x RTX 1000mg	Similar clinical efficacy after 2 years
YEAR	**OBSERVATIONAL STUDY**	**PATIENTS (n)**	**PATIENT CHARACTERISTICS**	**TREATMENT ARMS**	**OUTCOME**
2016	CERERRA collaboration (Chatzidionysiou et al.)	2873	Variable	RTX 2x 500mg RTX 2x 1000mg	• Both RTX regimes have comparable clinical outcomes at 6 months
2017	AIR registry (Henry et al.)	1278	RA treated with RTX standard dose	RTX 2X 1000mg. Later: 1) 2x RTX 1000mg 2) < RTX 2000mg	Reduced RTX dose (vs standard) showed: • Similar maintenance of treatment • Lower rate of serious infections • More cost-effective

Table 1. Trials comparing different doses of rituximab.

DANCER: Dose-ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis, MTX: methotrexate, RTX: rituximab, TNFi: tumour necrosis factor inhibitor, IV: intravenous, PO: per oral, ACR: American Colleague of Rheumatology, EULAR: European League Against Rheumatism, SERENE: Study Evaluating Rituximab's Efficacy in Methotrexate Inadequate Responders, MIRROR: Methotrexate Inadequate Responders Randomized Study of Rituximab, IMAGE: International Study in Methotrexate-Naive Patients Investigating Rituximab's Efficacy, CERERRA: The European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis, AIR: Autoimmunity and Rituximab registry

	ADVERSE EVENTS (AEs)		SEVERE AEs (SAEs)			ACUTE INFUSION REACTIONS			INFECTIONS			
	Overall	**Most common**	**Overall**	**Malignancies**	**Deaths**	**Overall**	**1st Infusion/ course**	**2nd Infusion/ course**	**Overall**	**Most common**	**Serious infections**	**Rate of serious infections per 100 patient-years**
DANCER (24 w)	Reported at least 1 adverse event: - Placebo → 70% - RTX 500 → 81% - RTX 1000 → 85% The majority (82%) in each group were mild to moderate	- IRRs - RA flares (most common in the placebo arm)	26 SAEs (20 of them were non-infectious) - Placebo → 3% - RTX 500 → 7% - RTX 1000 →7%	No malignancies	1 death in RTX 500 regime (cerebral infarction)	Most commonly associated with the 1st infusion of rituximab.	**1ST INFUSION** Overall for the first infusion: - Placebo →17% - RTX 500 →23% - RTX 1000 → 32% Without IV steroids as pre-medication: - Placebo →14% - RTX 500 →32% - RTX 1000 → 37% With IV steroids as pre-medication: - Placebo →19% - RTX 500 →19% - RTX 1000 → 29%	**2ND INFUSION** Without IV steroids as pre-medication: - Placebo →8% - RTX 500 →5% - RTX 1000 → 6% With IV steroids as pre-medication: - Placebo →7% - RTX 500 →2% - RTX 1000 → 8% With IV and PO steroids. - Placebo →16% - RTX 500 →12% - RTX 1000 → 9%	Similar type and severity - Placebo →28% - RTX 500 →35% - RTX 1000 →35%	- RTI - UTI - Nasopharyngitis	6 serious infections: - Placebo → 2 (1%) (Pneumonia, upper RTI) - RTX 500 → 0 - RTX 1000 → 4 (2%) (2 pyelonephritis bronchitis, epiglottitis)	- Placebo → 3.19 - RTX 500 → 0 - RTX 1000 → 4.74
SERENE (24 w)	Similar incidence of AEs and SAEs across all	- IRRs - RA flares - Nasopharyngitis - Upper RTI	Placebo →9% - RTX 500 →4% - RTX 1000 →15%	4 malignancies: - Placebo → 1 (lung adenocarcinoma)	No deaths	IRRs more frequent with the 1st infusion, especially in	**1ST INFUSION** Highest in the first infusion:	**2ND INFUSION** - Placebo- →8%	Infection rates (including serious): - Placebo →43%	- Nasopharyngitis -Upper RTI	- Placebo → 4 (2%) - RTX 500 → 1 (<1%) - RTX 1000 → 2 (1%)	- Placebo → 8.83 - RTX 500 → 1.26

	treatment arms			- RTX 500 → 1 (cervix ca.) - RTX 1000 → 2 (oesophageal and pancreatic (fatal))		the RTX 1000 arm. No serious IRR but 1 withdrawal in the RTX1000 arm	- Placebo →14% - RTX 500 →19% - RTX 1000 →25%	- RTX 500 →7% - RTX 1000 →6%	- RTX 500 →41% - RTX 1000 →36%			- RTX 1000 → 2.46
SERENE (48 w)	Overall safety profile similar in the 2 RTX arms	- IRRs - RA flares - Nasopharyngitis - RTI	- RTX 500 →8% - RTX 1000 →10%	- RTX 500 → 1 - RTX 1000 →2 (mentioned above)	2 deaths during the trial: - RTX 500 → 2 (Interstitial lung disease and abdominal sepsis) 3 deaths after withdrawal (one on each treatment arm): - Ventricular asystole - Cardiac failure - Pancreatic carcinoma	Overall 10-11% of patients had an IRR. None of them serious, but 2 withdrawals in the RTX1000 arm	**1ST INFUSION** - RTX 500 →13% - RTX 1000 →11%	**2ND INFUSION** - RTX 500 →4% - RTX 1000 →5%	Infection rates (including serious) remained consistent with the rates observed over the initial 24 weeks.	-Nasopharyngitis -Upper RTI	- RTX 500 → 3 (2%) - RTX 1000 → 3 (2%)	- RTX 500 → 2.62 - RTX 1000 → 1.96
MIRROR (48 w)	Similar incidence of AEs, SAEs and AEs across treatment arms	- RA flares - Nasopharyngitis - RTI - IRRs	- RTX 500 → 11% - RTX 500-1000 → 18% - RTX 1000 →17%	Malignancies (4): - RTX 500 → 1 (basal cell ca.) - RTX 500-1000 → 2(basal cell ca, squamous cell ca) - RTX 1000 → 1 (Hodgkin's disease)	No deaths	IRRs more frequent with the 1st infusion, of the 1st course. Overall: - RTX 500 → 39% - RTX 500-1000 →30% - RTX 1000→ 30%	**1ST COURSE** - RTX 500 → 33% - RTX 500-1000 → 23% - RTX 1000 →27% 4 serious IRRand/or CTC AE Grade 3 in the RTX500 group	**2ND COURSE** - RTX 500 → 18% - RTX 500-1000 → 15% - RTX 1000 →19% 1 serious IRRand/or CTC AE Grade 3 in the RTX500-1000 group	60% of patients reported at least 1 infection - RTX 500 → 56% - RTX 500-1000 →61% - RTX 1000→ 65% No opportunistic infections	-Nasopharyngitis - RTI - UTI	11 serious infections: - RTX 500 → 4 (sepsis, skin ulcer, lower respiratory tract infection and sinusitis) - RTX 500-1000 → 5 (bronchopneumonia, respiratory tract infection, post-operative wound infection) - RTX 1000→ 2 (diverticulitis, acute pyelonephritis)	- RTX 500 → 3.4 - RTX 500-1000 →4.7 - RTX 1000→ 2.4

IMAGE (52 w)	Similar incidence of AEs across all treatment arms	- Exacerbation of RA - IRRs	- Placebo →10% - RTX 500 →9% - RTX 1000 →10%	- Placebo → 5 - RTX 500 → 2 - RTX 1000 →1	Deaths (3): - Placebo → 3 (2 pneumonia, cerebral infarct)	IRR most frequent in the RTX1000 group for the 1st infusion of the 1st course. After that, similar in all groups	**1ST COURSE** - Placebo →12% - RTX 500 →14% - RTX 1000 →18%	**2ND COURSE** - Placebo →10% - RTX 500 →9% - RTX 1000 →10% (1 serious)	**3RD COURSE** - Placebo →6% - RTX 500 →2% - RTX 1000 →10%	2 opportunistic infections (PJP) -Placebo → fatal -RTX500→ resolved with treatment)	- RTI - UTI	More frequent in the placebo group: - Placebo →5% - RTX 500 →2% - RTX 1000 →3%	- Placebo → 6.09 - RTX 500 →4.61 - RTX 1000→ 3.73
SMART (24 w after the last RTX)	Similar incidence of AEs across all treatment arms	-Infections -IRR	- RTX 1000 → 29% - 2x RTX 1000 → 37%	- RTX 1000 → 6 - 2x RTX 1000 → 1 (not specified)	1 accidental death, not related to the study	Overall 15% of patients reported IRR (1 serious)	**1ST INFUSION** 15% had an IRR → 1 of them serious	**2ND INFUSION** 6% had an IRR		Infections reported in 56% of patients - RTX 1000 → 70% - 2x RTX 1000 → 59%	- Bronchitis - UTI - Gastroenteritis - Upper RTI	- RTX 1000 → 12% - 2x RTX 1000 → 3%	- RTX 1000 → 7.0 - 2x RTX 1000 → 1.7

Table 2. Safety information

DANCER: Dose-ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis, RTX: rituximab, RA: rheumatoid arthritis; SAEs: severe adverse events; IV: intravenous; PO: per oral; RTI: respiratory tract infection; IRR: infusion related reaction; SERENE: Study Evaluating Rituximab's Efficacy in Methotrexate Inadequate Responders, MIRROR: Methotrexate Inadequate Responders Randomized Study of Rituximab RTI: respiratory tract infection, UTI: urinary tract infection, CA: carcinoma; CTC AE: Common Terminology Criteria for Adverse Events; IMAGE: International Study in Methotrexate-Naive Patients Investigating Rituximab's Efficacy

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