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REVIEW ARTICLE

A comprehensive review of rituximab therapy in rheumatoid arthritis patients

Soheil Tavakolpour[1,2] · Samira Alesaeidi[2] · Mohammad Darvishi[3] · Mojtaba GhasemiAdl[2] · Sahar Darabi-Monadi[4] · Meisam Akhlaghdoust[5] · Somayeh Elikaei Behjati[6] · Arash Jafarieh[7]

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Abstract

Rituximab (RTX) is an approved treatment for rheumatoid arthritis (RA) patients that do not respond adequately to disease-modifying antirheumatic drugs. However, different new concerns, such as efficacy, optimum dose, safety issues, prediction of response to RTX, and pregnancy outcomes have attracted a lot of attention. The PubMed database was systematically reviewed for the last published articles, new findings, and controversial issues regarding RTX therapy in RA using "Rheumatoid arthritis" AND "rituximab" keywords, last updated on June 18, 2019. From 1812 initial recorders, 162 studies met the criteria. Regarding the optimum dose, low-dose RTX therapy (2 × 500 mg) seems as effective as standard dose (2 × 1000 mg), safer, and more cost-effective. The most common reported safety challenges included de novo infections, false negative serologic tests of viral infections, reactivation of chronic infections, interfering with vaccination outcome, and development of de novo psoriasis. Other less reported side effects are infusion reactions, nervous system disorders, and gastrointestinal disorders. Lower exposure to other biologics, presence of some serological markers (e.g., anti-RF, anti-CCP, IL-33, ESR), specific variations in *FCGR3A*, *FCGR2A*, *TGFβ1*, *IL6*, *IRF5*, *BAFF* genes, and also EBV-positivity could be used to predict response to RTX. Although there is no evidence of the teratogenic effect of RTX, it is recommended that women do not expose themselves to RTX at least 6 months before the conception. Only a reversible reduction of B cell-count in the offspring may be the pregnancy-related outcome. Although RTX is an effective therapeutic option for RA, more studies on optimum doses, prevention of RTX-related side effects, prediction of RTX response, and safety during the pregnancy are required.

Keywords Immunopharmacology · Pharmacogenetics · Pregnancy · Rheumatoid arthritis · Rituximab

✉ Soheil Tavakolpour
soheil.tavakolpour@gmail.com

[1] Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Rheumatology and Internal Medicine, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

[3] Infectious Diseases and Tropical Medicine Research Center (IDTMRC), department of aerospace and subaquatic medicine, AJA University of Medical Sciences, Tehran, Iran

[4] School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[5] Pars Advanced and Minimally Invasive Medical Manners Research Center, Pars Hospital, Iran University of Medical Sciences, Tehran, Iran

[6] Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

[7] Amir'Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease and also one of the most disabling types of arthritis, which is frequently observed among adults. Erosive joint damage, symmetric polyarticular inflammation, and functional impairments as the results of persistent inflammation are the most common complaints of RA patients. Disease Activity Score (DAS) is widely used as a measure of inflammatory disease activity in people with RA and is used to objectively evaluate a patient's response to treatment. The DAS28 is based on a count of 28 swollen and tender joints, with a score ranging from 0 to 9.4. A value of ≤ 3.2 was defined as the threshold for a low disease activity state and < 2.6 as the threshold for the remission [1].

Different types of autoantibodies, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), seem to be involved in the pathogenesis of RA. They are not only considered useful biological markers for the diagnosis of RA

but also have been suggested as predictors of drug responses in RA [2, 3]. A large number of risk factors have been suggested related to RA, such as sex, genetics, and epigenetic factors, as well as various environmental factors (e.g., smoking) which some of them were found to be associated with response to biological agents [4].

Considering the fact that RA is a progressive disease, accumulation of joint damage can cause irreversible disability, if left untreated or even improperly treated. Numerous RA patients all over the world are treated with conventional agents, such as glucocorticoids and methotrexate (MTX) [4]. Nonetheless, some of the patients may not tolerate them or even may not achieve disease remission. Although etiology and the pathogenesis of RA are complex, different newly employed biologics have revolutionized therapeutic approaches. They usually suppress the immune system by targeting particular signaling pathways and act in a more specific manner. It was suggested that biologic agents, such as tumor necrosis factor-alpha (TNFα) inhibitors and rituximab (RTX) could significantly reduce mortality risk in RA patients, as compared to the disease-modifying antirheumatic drugs (DMARDs) [5]. RTX, a chimeric anti-CD20 monoclonal antibody, depletes B cells through different mechanisms, including apoptosis of B cells, complement-dependent cytotoxicity, and mediation of antibody-dependent cellular cytotoxicity [6]. To date, the role of different arms of the immune system during the RA have remained largely unknown. However, achieving clinical remission in patients following B cell depletion confirmed the previous findings related to the critical roles of the humoral immune system in the pathogenesis of RA [7, 8].

During the last two decades, an increasing amount of evidence for the efficacy of RTX in RA patients has made this drug an attractive topic for several researchers and clinicians. Promising results of using RTX in RA patients had led to approving RTX by the Food And Drug Administration (FDA) with concomitant MTX for the treatment of moderate-to-severe RA on March 1, 2006 [9]. From that date, several studies had reported the significant reduction in DAS28 score and improvement of Health Assessment Questionnaire (HAQ), with no serious adverse events. This is consistent with the high efficacy and safety profile of RTX in RA patients [10–15]. Overall, among the different biologic drugs to target B cells, such as ocrelizumab, ofatumumab, belimumab, and atacicept, RTX is the only one with promising results and acceptable safety profile for the treatment of RA patients. Despite the approval of RTX for RA patients, promising results, and less adverse effects as compared to the conventional treatments, there are growing concerns over the safety of this drug. Additionally, there is no consensus regarding optimum dosage, biomarkers for RTX response, and treatment of pregnant women with RTX, which need to be addressed. Having a comprehensive insight into these matters could open an avenue for developing more effective and safer treatments for RA patients.

Search strategy and selection criteria

The PubMed database was searched for any study associated with the RTX in RA. Accordingly, two terms of "Rheumatoid arthritis" AND "Rituximab" were used to find relative studies. The search result was updated on June 18, 2019. The references for the selected articles were also checked for any missed articles.

Characteristics of included studies are listed below

- The original study in the English language.
- Association with using RTX in RA.
- Presentation or confirmation of a unique/novel clinical outcome(s), a biomarker for RTX response, specific recommendation, and any protocol of treatment. Critical meta-analyses and systematic reviews, which help to reach a clear message regarding uncertain issues as well as case reports with novel findings had been included.

After identification of studies, eligible studies were carefully read to extract any novel data regarding efficacy, safety, treatment protocol, RTX response's biomarker, and use of RTX in RA patients during the pregnancy. In the case of very repetitive results, which were confirmed by several studies, only those with higher number of patients, more clear message, and a higher quality of study design had been chosen and discussed.

Results

Among the 1805 found records in database searching, in addition to seven identified articles through searching in the reference list of full-text studied articles, 1369 records were selected for initial screening. Subsequently, 1161 records excluded due to presenting not original findings ($n = 629$), non-English studies ($n = 188$), and irrelevant data to using RTX in RA ($n = 344$). Reading the full-text of 208 studies had led to including 162 studies, which met the inclusion criteria. The reasons for exclusion of 46 ignored studies were the lack of association with RTX or RA ($n = 17$), not informative/novel data ($n = 26$), and no clear message ($n = 3$). The most important findings of such studies have been categorized into some major groups, including efficacy, optimum RTX doses, safety concerns, prediction of RTX response, and outcome of exposing pregnant RA patients to the RTX; and have been discussed in details. The study selection process and reasons for exclusions are presented in Fig. 1.

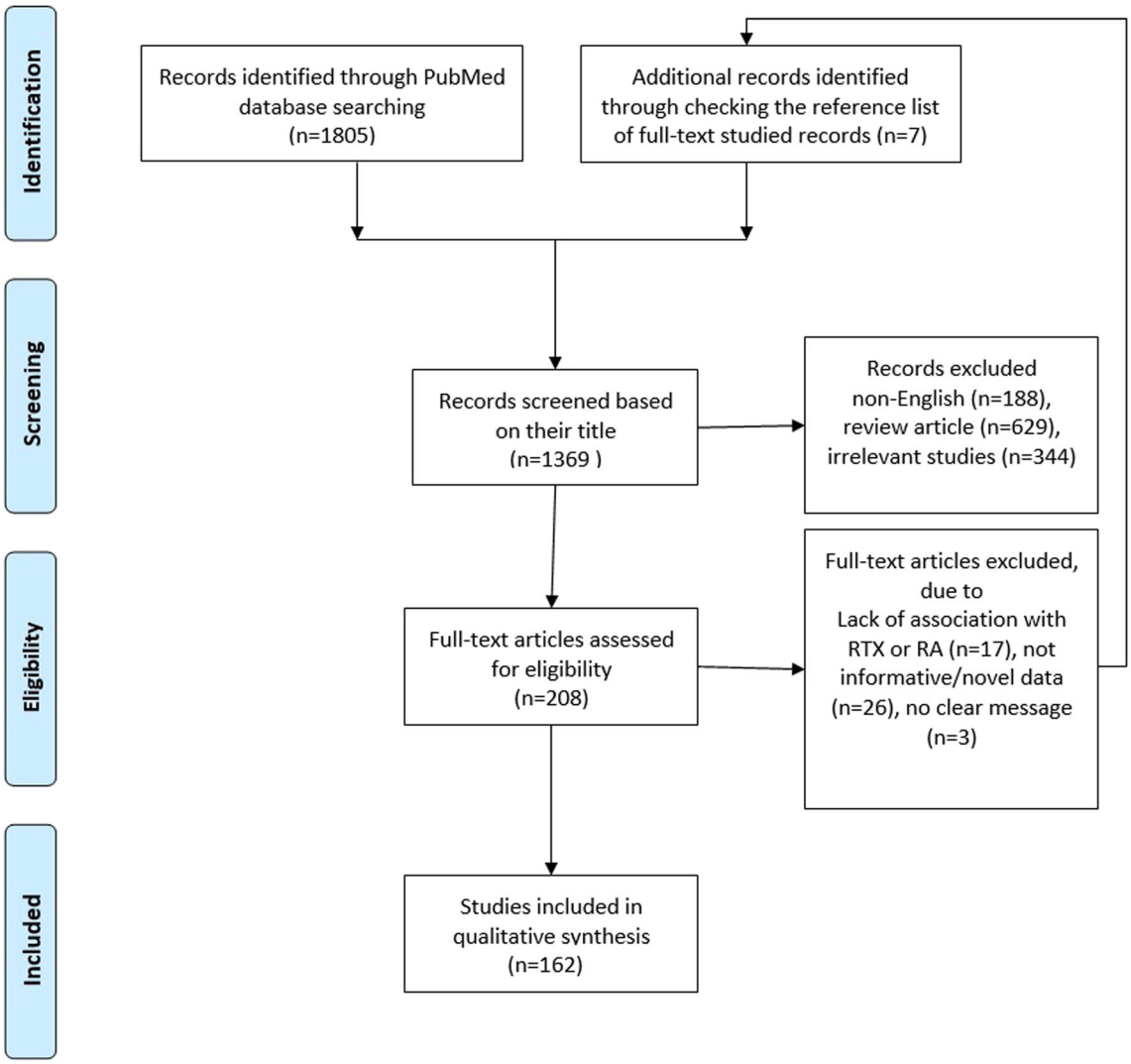

Fig. 1 The study selection process

Efficacy

Some years after the introduction of RTX, different studies showed its efficacy in refractory and active RA patients [16–18]. On those years, the high efficacy of RTX was reported in various studies. For example, Moore et al. [19] demonstrated a successful induction of clinical remission in a small number of patients. Employment of RTX plus MTX in patients with active disease and a history of inadequate response to at least one anti-TNF agent was another innovative attempt [15]. As the results, it was shown that a single course of RTX (2 × 1000 mg) with concomitant MTX therapy could significantly improve the clinical feature of RA patients within 24 weeks. Subsequently, using RTX as an alternative treatment in anti-TNF therapy-resistant RA patients was encouraged in several other studies [20–22]. However, Porter et al. [23] conducted a multi-center open-label randomized non-inferiority trial and demonstrated that initial treatment with RTX is non-inferior to initial treatment with anti-TNF agents in RA patients. In addition to the significant reduction of DAS28 [15], RTX was shown to be effective in reducing radiographic damage [24, 25]. It also caused a significantly improvment in the HAQ disability index [14]. Additionally, refractory RA patients experienced significant improvement in patient-reported outcomes, such as patient global, pain, and fatigue, 1 year after initiating RTX [26]. It was also shown that RTX is significantly more effective than abatacept in a 2-year follow-up of outcomes [27].

Recently, it was found that RTX could be even more effective in some cases than we thought. For example, following three consecutive RTX courses, 9 years of sustained biologic-free clinical remission as the results of persistent peripheral B cell depletion was reported [28]. However, in spite of frequently reporting of complete B cell depletion followed by clinical improvement of RTX-exposed patients [18], some evidence implying to the inability of RTX incomplete depletion of synovial or bone marrow $CD19^{+}$ B cells number in few patients, which is probably followed by non-favorable clinical responses [29–31].

After general acceptance of the efficacy of RTX in RA patients, the influence of response to previous treatments, especially anti-TNF agents has become another hot topic among the researchers. It was suggested that naïve patients for biological drugs might be better RTX responders [32]. Moreover, a higher failure of the previous anti-TNF agents or even previously exposure to them seem to be associated with a less favorable response [32–35]. In this regard, it was observed that those with a lower number of previously failed TNF blockers usually experience a more favorable clinical response following RTX therapy [36]. However, the association between the numbers of previously failed attempts with anti-TNF agents was not confirmed in the later study with a higher number of RA patients [37]. Additionally, Soliman et al. [22] suggested that non-responders to at least one anti-TNF agents might benefit more from switching to RTX than switching to alternative anti-TNF therapy. Concomitant MTX was also suggested as a predictor of low disease activity/remission at 24 months [38].

In 2011, it was speculated that a history of treatment with statins might be related to less efficacy of RTX in RA patients [39]. However, this belief did not last long and was revised by later studies. Considering the fact that age is usually higher in patients receiving a statin, Das et al. [40], suggested the probable involvement of ages of patients. Subsequently, other authors with a long-term follow-up did not find any association between RTX clinical efficiency and concomitant use of statin [41, 42]. The key points related to RTX efficacy are summarized in Table 1.

Initial and maintenance doses of rituximab in rheumatoid arthritis

Before approval of RTX for RA patients, different researchers have designed studies to show its high efficacy in refractory and seropositive active RA patients, while there was no consensus on the optimal dosage and schedule [16–18]. After evaluation and designing several studies, the licensed dose of RTX in RA was introduced as the two intravenous infusions of 1000 mg, given 2 weeks apart (days 1 and 15). However, different other RTX doses were tested to assess efficacy, safety, and cost analysis. One of the most attractive strategies was comparing the effectiveness and safety of standard dose (2 × 1000 mg) with low-dose of RTX (2 × 500 mg). In comparing RTX therapy with a low-dose regimen and standard dose, no significant difference in either clinical or safety outcomes was detected [43, 44]. Moreover, in Phase III randomized study, efficacy, and safety could not be clearly differentiated between the RTX at low-dose and standard dose [45]. These findings were also confirmed in a meta-analysis, containing eight studies. As the results, the low-dose regimen of RTX regimen not only a resulted in similar effectiveness but also it was associated with a lower cost [46]. The same findings have also been reported in the next updated meta-analysis [47]. As another attempt, treating RA patients with a standard dose and reduced doses (a total dose lower than 2000 mg) have revealed no significant difference between the strategies when maintenance of RTX at 5 years was evaluated [48]. Additionally, the total cumulative doses of RTX, as well as the rate of serious infections were found to be significantly lower in the reduced-dose group [48]. In accordance with some of the studies, it seems that cumulative doses of the second course of RTX therapy could be lower than the standard dose, with no impairment in drug efficacy. It probably leads to more cost-saving and is associated with a lower rate of severe adverse events [49, 50].

In addition to trying to find optimum doses, the difference between the efficacy of fixed-interval RTX retreatment and on-flare retreatment as well as the influence of a number of RTX courses is another critical issue. Regarding the former topic, there is some controversy. In fact, in a cohort study containing a large number of patients, evaluation of DAS28 showed that a fixed-interval retreatment group yielded significantly better results than the on-flare group [51]. However, in a recently published study with a lower number of patients, it was reported fixed-interval strategy does not lead to better disease control or more drug use compared to on-flare retreatment strategy [52]. Meanwhile, more studies had been conducted to address the latter issue. Vital et al. [53] proposed that an extra 1000 mg infusion of RTX at 4 weeks improves the levels of B cells depletion in those who show incomplete B cell depletion. As it was expected, complete depletion led to better clinical response without any additional safety concern. In a trial containing more than 1000 RA patients exposed to

Table 1 Overview of rituximab efficacy in rheumatoid arthritis patients

RTX efficacy	- RTX could be an effective therapeutic option in patients with inadequate/no response to anti-TNF agents [20–22]. - RTX is capable of long-lasting remission [28]. - Lack of complete depletion of B cells may occur in some patients following RTX [29–31].
Influence of anti-TNF agents	- There is strong evidence to support the contrary association of previous exposure to anti-TNF agents, response to RTX, and the association of less failure of previous anti-TNF agents with higher response rate [32–35].
Influence of statins	- Statins do not seem to influence RTX efficacy directly [40–42].

RTX, rituximab; *TNF*, tumor necrosis factor

RA, it was suggested that repeated courses of RTX could be associated with sustained clinical responses with no new adverse events [54]. Additionally, non-responders to the first RTX cycle may benefit from early retreatment with RTX [55]. It is worthy to note that the administration rate of RTX could even be faster at the second and subsequent infusions with no concern related to increasing the rate or severity of infusion-related reactions [56]. The key points related to initial RTX doses and retreatment are briefly brought in Table 2.

Safety concerns

Generally, RTX administration in RA patients has been accepted as a safe procedure, and prolonged exposure to RTX does not seem to be related to additional adverse events [10–13, 20]. However, there are some increasingly concerns related to the safety profiles of RTX in RA patients, such as development/reactivation of infections, failure of immunization, and paradoxical reactions. Table 3 summarizes the most critical points related to the RTX safety profiles.

Infections

Development of de novo infections has been recognized as the most challenging RTX-related side effects. Recently, infection rates (both serious and non-serious) were reported 0.30 to 0.41 per patient-year [79]; and between 0.058 and 0.089 per patient-year reported in different studies for significant infections [57, 58]. In a study with 989 RA patients and a mean of 3.9 years follow-up, the rate of infection was reported 20%, which 8% of patients had ≥ 2 significant infections, and 1.6% of them expired due to infection [57]. Interestingly, in a study with a large number of patients by the French Society of Rheumatology, around half of the most common RTX-related severe infections in RA patients occurred within the first 3 months [59]. In another study, containing 3363 courses of RTX, the risks of serious infections were highest within the first 6 months after RTX start [58].

It is worth to note that observations of Silva-Fernandez et al. [80] suggest that serious infections related to anti-TNF agents are comparable to RTX in non-responders to TNF blockers within the first year of follow-up. In a recently conducted systematic review, it was concluded that RTX treatment has no additional risks for infections over non-RTX treatment in RA patients [81].

Less frequently reported safety concerns following RTX therapy in RA patients across the literature includes *Campylobacter* fetus infection [82], tuberculosis arthritis [83], *Pasteurella multocida* infection [84], bronchiectasis [85], and progressive multifocal leukoencephalopathy (PML) [86]. In another study, which reported seronegative West Nile virus in RA patients under treatment with RTX, it was warned that RTX not only predisposes patients to the infections but may also lead to a false negative serologic test of viral infections, which is expected to follow by delayed diagnosis [60]. RTX in RA may also cause a delay in clearance of some infections, such as *Babesia microti* infection [61]. Additionally, late-onset neutropenia might occur after RTX administration and might lead to serious infections [87].

Regarding prediction of severe infection risk, higher age, higher body mass index (BMI), diabetes condition, and presence of infection during the last years before RTX administration, RA-related extra-articular involvement, lung and cardiac comorbidities as well as low baseline IgG level (< 6 g/l) has been suggested [57, 59]. However, increasing in cumulative dose of RTX did not cause a higher incidence of significant infections [57].

In addition to the development of new infections, reactivation of chronic infections (e.g., hepatitis B virus [HBV]) is a problematic issue. Reactivation of chronic HBV (CHB) after exposure to RTX is one of the most critical concerns [88]. In addition to HBsAg positive patients, those with resolved or occults HBV (HBsAg−/anti-HBc+) are also at the risk of HBV reactivation [62–64]. This phenomenon was reported with the incidence of 9.1% among the HBsAg−/anti-HBc+ patients within the mean duration of 25.4 ± 4.6 months from the first RTX infusion [65]. In another study, the incidence of HBV reactivation was reported by 8.7%, during the mean 61 months from the first RTX infusion in HBsAg-negative patients [66]. In contrast, in a retrospective multicenter Italian study, a very low risk of HBV reactivation was noted as the result of RTX administration [89]. Similar to the CHB infected patients, there is also some evidence of the capability of RTX in the induction of hepatitis C virus (HCV) reactivation [67, 68]. There are also pieces of evidence that during the RTX treatment in rheumatic diseases, including RA, clinicians

Table 2 Overview of optimum doses and retreatment of rheumatoid arthritis patients with rituximab

RTX doses	- The standard dose of RTX (2 × 1000 mg) probably needs to be revised. - Low-dose of RTX (2 × 500 mg) is effective and safe alternative dose in RA patients [43, 44, 46, 47]. - Less cumulative doses of RTX seems to be not only cost-effective but also safer [48].
Repeated doses of RTX	- Patients with incomplete response to RTX in seem to benefit from additional courses of RTX [54, 55]. - Repeated/maintenance doses of RTX in RA patients could be tolerated, and it does not seem to associate with additional adverse events [54, 56].

RTX, rituximab; *RA*, rheumatoid arthritis

Table 3 Overview of safety concerns in rituximab-treated patients with rheumatoid arthritis

Infection	- RTX increase the risk of de novo infections, false negative serologic tests of viral infections, and cause delay in clearance of some infections [57–61]. - Reactivation of chronic HBV and HCV may occur after the exposure to RTX; prophylaxis should be initiated for patients at high risk [62–68].
Immunization	- RTX therapy during the first six-month after the influenza vaccine may interfere with the development of new specific antibodies [69, 70]. RTX also was found to be associated with impaired response to hepatitis B vaccination [71]. Thus, vaccination is better to be planed before RTX administration.
Paradoxical reaction	- Development of new immune-related disorder, especially psoriasis may occur following RTX therapy [72–77].
Other side effects	- Patients exposed to RTX may be at the risks of infusion reactions, nervous system disorders, gastrointestinal disorders, and general disorders; more rarely, severe anaphylactic reaction [9, 23, 78].

RTX, rituximab; *RA*, rheumatoid arthritis; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus

should be aware of a potential, albeit modest, risk of developing progressive multifocal leukoencephalopathy (PML) [86]. It is a demyelinating disease of the central nervous system caused by the John Cunningham (JC) virus. RTX was found to be associated with the highest risk of PML development among the biologics used for RA treatment [90].

Surprisingly, there are some reports of successful administration of RTX in patients under the risk of reactivation of certain types of infections or even those who were suffering from a reactivated infection following other treatments. A decade ago, the first report of efficiently and safely using RTX in an RA patient who had developed tuberculosis (TB) as the results of the anti-TNF agents was reported [91]. The safety of RTX in treating RA with concomitant pulmonary TB was also reported in another study [92]. Moreover, two cases with active TB have been reported, who reached not only RA remission but also experienced inactivation of TB following the RTX treatment [93]. As another surprising finding, it was reported that RTX eradicates all traces of Epstein-Barr virus (EBV) [94].

Immune response to vaccine antigens

In addition to the risk of development or reactivation of infections following the weakening of immune responses, successful immunization is another challenging issue related to RTX therapy. It was demonstrated that few RA patients exposed to the RTX may not be sufficiently protected against influenza infection, while it could be effective in the majority of patients [69, 70, 95]. The total absence of influenza-specific IgG production was also reported in around half of the patients, exposed to RTX 6 months before vaccination [69]. However, the impaired humoral immune responses against influenza seem to modestly restore within 6–10 months after the last infusion [70]. Regarding hepatitis B vaccination, although the hepatitis B vaccination did not lead to increasing the rate of RA flare, and RA patients well-tolerated, RTX was associated with impaired response to hepatitis B vaccination [71].

Paradoxical reactions and rare side effects

One of the most frequently reported paradoxical effect related to RTX therapy in RA patients is related to the development of psoriasis, a T cell-mediated autoimmune skin disease. In the first year after the approval of RTX by FDA, an unexpected and serious paradoxical reaction was reported. Dass et al. [72] have reported three patients with no known risk factor for psoriasis, who developed psoriasis as the result of RTX therapy. Interestingly, the underlying disease well-responded to RTX in all the patients. After that, the development of psoriasis was reported in more patients by other authors [73–75]. Plantar pustulosis development following successful treatment with RTX in RA patients was also reported [76]. In contrast to these results, evaluation of a large number of patients supports a causative role of RTX in neither new-onset nor flare of preexisting psoriasis in RA patients [96]. It is worthy to note that RTX-specific psoriasis may also occur with anti-TNF therapy. In fact, despite the indicated for the treatment of psoriasis, anti-TNF agents may paradoxically trigger a psoriasiform condition [97]. Other less frequent reports of paradoxical effects include de novo ulcerative colitis developing probably due to RTX administration in RA patients [77], progressive reduction of lung function parameters, and some lung-related side effects, such as interstitial lung diseases have been reported as paradoxical or rare side effects of RTX therapy [98, 99].

Other side effects

In addition to the infections and infestations, which have been frequently reported in RA patients exposed to RTX, and rare reports implying the paradoxical reactions, different other adverse reactions also seem probable. Infusion reactions (e.g., headache, skin itchiness, throat irritation) which usually are mild to moderate in severity, could appear in approximately a quarter of patients [9, 78]. It has been suggested that cytokine-release plays a crucial role, and CD20 cells, as well as CD16 positive natural killer (NK) cells, are involved in infusion

reaction [100]. Recently, it was proposed that anti-CCP positivity and absence of concomitant treatment with a synthetic DMARDs increase the risk of serious infusion-related reactions [101].

In a study containing 144 RTX-exposed RA patients, the frequently observed adverse reactions (> 20%) include nervous system disorders, gastrointestinal disorders, and general disorders and administration site conditions [23]. Additionally, a significant decrease in bone mineral density (BMD) at the femoral neck and total femur, but not in bone density at the lumbar spine or ultra-distal forearm was reported following 12 months follow-up in RTX-exposed refractory RA patients [102]. Increased risk of hypogammaglobulinemia as the result of RTX administration in RA patients is another challenging issue [103]. The main risk factors for hypogammaglobulinemia after B cell-targeted therapy in the autoimmune rheumatic disease was found a low baseline serum IgG levels [104]. Thus, the use of prophylactic intravenous immunoglobulins (IVIg) and IgG monitoring may be useful for those receiving RTX. Furthermore, recently, a severe anaphylactic reaction to RTX in two patients was also reported [101]. These side effects, such as sustained secondary antibody deficiency should be considered for evaluation of risk to benefit of RTX in RA patients [104].

Probable allowable conditions for rituximab therapy

Although RTX is related to different safety concerns, there is some evidence of safe administration of RTX in specific groups of RA patients. For example, low-dose RTX (2 × 500 mg) was safely used in a 76 years old man with heart failure (HF), which did not lead to aggravation of HF status [105]. Moreover, RTX was effective and safe in the treatment of subcutaneous nodulosis in an RA patient [106]. Moreover, no relation between surgical complications and RTX administration in RA patients was reported [107].

Some of the potential long-term side effects of RTX had been checked in some studies, which suggest RTX not a risk for increased risk of future incident malignancy in RA patients [78, 108, 109]. Moreover, evaluation of chromosomal changes in patients exposed to the RTX was associated with neither clastogenic nor aneugenic effects [110]. Interestingly, the beneficial role of RTX in not only controlling RA activity but also resolving drug-induced lupus as the result of treatment with anti-TNF agents was observed [111].

Predition of response to rituximab

Despite the several reports implying high efficacy of RTX therapy in a large number of patients, many of them do not respond, and different patients may experience related adverse events. For example, in the recent study with 1629 RA patients who continued RTX for more than 4 years, 240 (16%) discontinued RTX treatment because of ineffectiveness and 95 (5.8%) for adverse events [112]. Over the last decade, we have witnessed rapid progress in the prediction of response to the particular therapeutic options in autoimmune diseases, such as RA [113, 114]. Although several pharmacogenetics studies have been conducted [115], we still could not consider it very practical. However, to date, different markers, including serological, cells numbers, genes expression, and genetic variations have been suggested, which discussed below. Despite the suggestion of several markers for prediction of RTX response in RA patients, only a few of them are routinely used by the majority of rheumatologists. Table 4 summarizes some of the most important predictors of a better response to RTX.

Cell counts

Considering the RTX mechanism of action, it is expected that patients with complete and rapid depletion of B cells benefit more from the RTX; however, there are conflicting results. As one of the first studies related to the prediction of response to RTX, Dass et al. [143] measured peripheral B cell numbers using minimal residual disease (MRD) flow cytometry before and after each infusion. They have concluded that a lack of complete depletion of $CD20^+$ cells following the first infusion is associated with a poorer outcome. However, other groups did not find any relationship between B cell depletion and clinical response in RA patients exposed to RTX after either tissue examination, using flow cytometry, immunohistochemistry, and quantitative PCR or blood examination by fluorescence-activated cell sorting [144, 145]. Additionally, baseline or post-treatment frequencies of activated T cells do not seem to be a predictor of treatment response [145].

A higher number of circulating pre-plasma cells (cells that usually do not express CD20 and cause resistance to RTX) at the baseline were also related to not responding to RTX as well as incomplete depletion of B cells [31]. A higher elimination rate constant of RTX (the rate at which RTX is removed) was significantly associated with the $CD19^+$ count as well as IgG concentration [146]. However, Sellam et al. [147] reported comparable levels of $CD19^+$ B cells among the responders and non-responders to RTX. Association of low baseline $CD27^+$ memory B cell frequency, normal levels of RF^+CD19^+ and increased levels of $CD19^+CD27^-IgD^-$ B cells are other reported biomarkers to predict response to RTX in RA patients [147, 148]. Baseline $CD95^+$ pre-switch B cells frequency were also observed as a negative predictor of response to RTX [149].

Not only B cells but also T lymphocytes and other immune cells seem to be involved in RTX response. For example, total lymphocyte counts and $CD4^+$ T cells at baseline were found as the independent predictors of EULAR response [116]. In addition to higher baseline levels of the total lymphocytes, higher plasmablast frequency (> 2.85%) at the baseline was

Table 4 Predictor of better response in rituximab-treated patients with rheumatoid arthritis

Cells	- The lower number of circulating pre-plasma cells [31] - Lower plasmablast frequency [116] - Lower CD4+ T cells [8, 117] - Higher frequency of iNKT cells [118–120]
Serology	- Higher titers of autoantibodies (RF, anti-CCP-positive) [32–34, 121–126] - Probably $detec_{table}$ serum levels of IL-33 [122] - Lower baseline value of ESR [127]
Genetic polymorphisms	- rs1800795 C/G,G/G (*IL6*) [128] - rs1800470 C/T (*TGFβ1*) [129] - rs1800471 G/C (*TGFβ1*) [129] - rs9514828 C/C (*BAFF*) [130] - rs2004640 T/G (*IRF5*) [131] - rs396991 G (*FCGR3A*) [127, 132–135] - rs9514828 C (*TNFSF13B*) [131] - rs1801274-TT (*FCGR2A*) [127]
Genes expression	- Low or absent of baseline IFN type I response genes (IRGs) expression [136, 137] - Lower expression of *ARG1* in CD4+ T cells [138] - Higher expression of *TRAF1* in whole blood [138] - Higher expression of *TLR4* in CD4+ T cells [138]. - miR-125b overexpression [139] - Decreased in the expression of mTOR, p21 (*CDKN1A*), caspase 3 (*CASP3*), *ULK1*, *TNFα*, *IL-1β*, and cathepsin K (*CTSK*) [140]
Other biomarkers	- EBV-positive patients [94, 141] - Lower baseline DAS28 [38, 142]

also able to sensitively identifies RA patients who will not benefit from RTX. Because depletion of substantial T cell, particularly $CD4^+$ cells is one of the outcomes of RTX infusion and probably is associated with the clinical response, monitoring of T cells could be considered one of the possible approaches to early detection of likely non-responders [8, 117]. Indeed, a significant reduction in the circulating $CD4^+$ T cell may increase the chance of responding to RTX. Innate immune system's components are also involved, and a lower count of NK cells and also a higher frequency of iNKT cells could predict a better response to RTX in RA patients [118–120].

Serological markers

During recent years, three markers of total IgG serum concentrations, RF, and anti-CCP in RA patients with the aim of predicting response to RTX have been widely studied. Regarding the association between the elevated baseline IgG serum concentrations and a better response to RTX, there are conflicting data. Some studies have shown it as a predictor of RTX response [121, 122], while some others do not agree [123, 147]. A higher titer of all autoantibodies at the baseline was found to be related to a better response to RTX in RA patients [150].

Majority of studies implying a higher efficacy of RTX therapy in patients with both positive RF and anti-CCP as compared to seronegative patients [32–34, 121–126]. However, there are some other pieces of evidence, which only suggest one of the RF or anti-CCP as the marker of clinical response [36, 123, 127, 147]. Recently, RTX discontinuation (mainly as the result of ineffectiveness, 46%; and death, 24%) was associated with RF negativity [112]. The lower baseline value of erythrocyte sedimentation rate (ESR) is another suggested factor prediction be a better response to RTX [127]. Multi-bio-marker disease activity (MBDA) score, which is calculated by measuring 12 serum proteins and clinically validated as a measure of disease activity in patients with RA was found to be valid for tracking disease activity in RA patients treated with RTX [151]. Moreover, change in MBDA score reflected the degree of treatment response [151]. In contrast, no correlation was found between the response to RTX and neither baseline B cell-activating factor (BAFF) level and BAFF-R expression nor 25(OH)D levels in RA patients [152, 153]. Detectable serum level of IL-33 was found to be associated with EULAR responders to RTX [122]. However, no association between IL-33 detection and response to RTX was found in another study [154].

Genetic markers

One of the most attractive markers in pharmacogenomics of autoimmune diseases is genetic polymorphisms [115]. Genetic polymorphisms in different genes have been found to be associated with treatment response and might be considered a predictor for both efficacy and safety profile of RTX therapy. Since cytokines orchestrate the fate of autoreactive lymphocytes and autoimmune reactivity, their polymorphisms have attracted the attention of many researchers owing to their potential applications in the prediction of treatment response to RTX. It was demonstrated that patients with GC/GG genotypes in interleukin (IL)-6 promoter at position -174 (rs1800795) were more susceptible to a better response at month + 6 as compared to those with CC genotypes [128]. SNPs at *TGFβ1* codon 10 (rs1800470) and *TGFβ1* codon 25 (rs1800471) are other associated polymorphisms with clinical response to RTX [129]. Indeed, it was observed that CT genotype for rs1800470 and GC genotype for rs1800471

could be the criterion of response to RTX therapy in RA patients [129]. BAFF is a cytokine essential for B cell maturation, which significantly contributes to the pathogenesis of different autoimmune diseases [155]. Although there was no relation between the *BAFF*−871 promoter polymorphisms (rs9514828; C>T) and BAFF serum level in RA patients, homozygous carriers of the *BAFF* rs9514828 C were found as better responders to RTX as compared to the homozygotes for *BAFF* rs9514828 T (response rate: 92% for C/C vs. 64% for T/T) [130].

Polymorphisms in *FCGR3A* gene is another interesting research topic. In fact, the variations in this gene influencing the outcome of B cell-depleting therapy with RTX in malignancies, probably through the induction of differential affinity of the receptors [156]. Regarding RA, *FCGR3A* F158V (rs396991; T>G) polymorphism seems to contribute to having a higher response rate to RTX. In fact, those with V allele (code Valine) and/or G allele were found to be better responders in different studies conducted in North America [132], France [133], Italia [134], Hungary [135], and Spain [127]. The presence of *FCGR2A* rs1801274-TT genotype is another novel probably involved factor in RTX response in RA patients [127]. Additionally, *IRF5* rs2004640 and *TNFSF13B* rs9514828 influenced response to RTX at week 24 [131]. Association between the RTX response and the allele*2 of the HS1,2A enhancer in seropositive RA patients was also reported [157].

The role of genetics in the prediction of response to RTX is not limited to the genetic polymorphisms. Different studies have evaluated genes' expression in responders and non-responders. Low or absent baseline IFN type-I response gene (IRG) expression levels (consist of *LY6E*, *HERC5*, *IFI44L*, *ISG15*, *MxA*, *MxB*, *EPSTI1*, and *RSAD2*) means better response to RTX in RA patients [136, 137]. In a small cohort study containing nine RA patients, it was found that lower expression of *ARG1* and a higher expression of *TRAF1* in whole blood and *TLR4* in $CD4^+$ T cells were associated with better response to RTX [138]. As the results of another study, the response to RTX was associated with a decrease in the expression of mTOR, p21 (*CDKN1A*), caspase 3 (*CASP3*), *ULK1*, *TNFα*, *IL-1β*, and cathepsin K (*CTSK*) [140]. Moreover, increased CD46 expression, but not CD35, seems to be able to predict time to the repopulation of B cells in RA patient treated with RTX [158]. In contrast to leukemia B cells [159], the alternative CD20 transcript could not predict resistance to RTX in RA patients [160]. High serum levels of miR-125b, which are overexpressed in RA patients, increase the success of the response to RTX [139].

Other biomarkers

As it was discussed, being naïve to biologics [32] or a smaller number of previous biological therapies [127] are associated with better response to RTX. Some studies have highlighted the positive role of the presence of EBV genome in responding to RTX. Indeed, RA patients who are also EBV carriers not only respond better to RTX therapy but also need an additional course of treatment within a longer time [94, 141]. However, this did not confirm in a later conducted study [123]. Smoking is another suggested factor that influences RTX response. Active smokers, especially those with negative auto-antibody status were found to be more susceptible to not respond to RTX [125], but this was not found in another study [142]. Additionally, lower baseline DAS28 was found as an independent predictor of good EULAR response at 6 months [142] and 24 months [38].

Pregnancy and fetal risk

Despite the several conducted studies on the efficacy and safety of RTX in RA patients, there are few data concerning risk assessment of RTX therapy in pregnant women. A study on pregnant animal models (macaque species) exposed to RTX had shown no evidence of teratogenic effects, but only a reversible reduction of B-cell count in the offspring [161]. Since RTX is an IgG-based antibody, it could cross the placental barrier, which increases as pregnancy progresses and may lead to increased susceptibility to infections through impairing fetal and neonatal B cell development [162]. Hence, different studies have recommended stopping RTX therapy at least 12 months before starting a pregnancy [163]. However, it seems that the RTX administration before conception is safer than we thought [164]. According to the EULAR recommendation, RTX probably does not increase the rate of congenital malformations; even in exceptional cases, RTX usage was allowed early in gestation [165]. However, in later stages of pregnancy, the risk of B cell depletion and other cytopenias in the neonate had been warned. However, according to the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR-BHPR) guideline, RA patients should not be exposed to RTX, at least 6 months before conception [166]. However, inadvertent pregnancy may occur during or after RTX treatment. Thus, it is recommended that before starting RTX infusion, all women of childbearing age must take a pregnancy test before RTX administration; those with a positive result must avoid RTX therapy. Additionally, women of childbearing age are advised to use effective contraception for 6 months after the last infusion of RTX [167].

Recently reported records from the British Society for Rheumatology Biologics Register on pregnancy outcomes in RTX-exposed RA patients (BSRBR-RA) are registering 66% ($n = 6$) live births, 22% ($n = 2$) miscarriages/stillbirths, and 11% ($n = 1$) termination among expecting mothers, who had been exposed to RTX within 6 months of conception [168]. These records change to 86% ($n = 6$), 14% ($n = 1$) and 0% of

live births, miscarriages/stillbirths, and termination, respectively, for those who had been exposed to RTX between 6 and 12 months before conception. Surprisingly, the safety of RTX administration within the first trimester of pregnancy in two RA patients was also reported [169]. This unexpected outcome was explained by very low transplacental maternofetal transfer of this monoclonal antibody during the first trimester of pregnancy. In eight pregnancies that occurred during a study for evaluation of the safety of RTX, except two spontaneous abortions, one elective termination, and one preterm birth, others were successful and no congenital abnormality was found [57]. As EULAR had recommended, due to the lack of evidence regarding RTX in breast milk, patients must avoid exposure to the RTX in breastfeeding [165].

Rituximab biosimilars

During recent years, different RTX biosimilars have been introduced, and many clinical trials are being conducted to evaluate their efficacy and safety, and compare to originator [170]. These alternative drugs, such as Truxima (CT-P10) and Rixathon (GP2013) are increasingly being used due to availability and lower cost. It was shown that switching from reference RTX to GP2013 is not associated with any additional safety and immunogenicity problems [171]. Regarding CT-P10, there was no significant difference between the efficacy, safety, and immunogenicity of reference RTX and biosimilar RTX in 24, 48, and 72 weeks follow-up [172–174]. The similar findings in term of

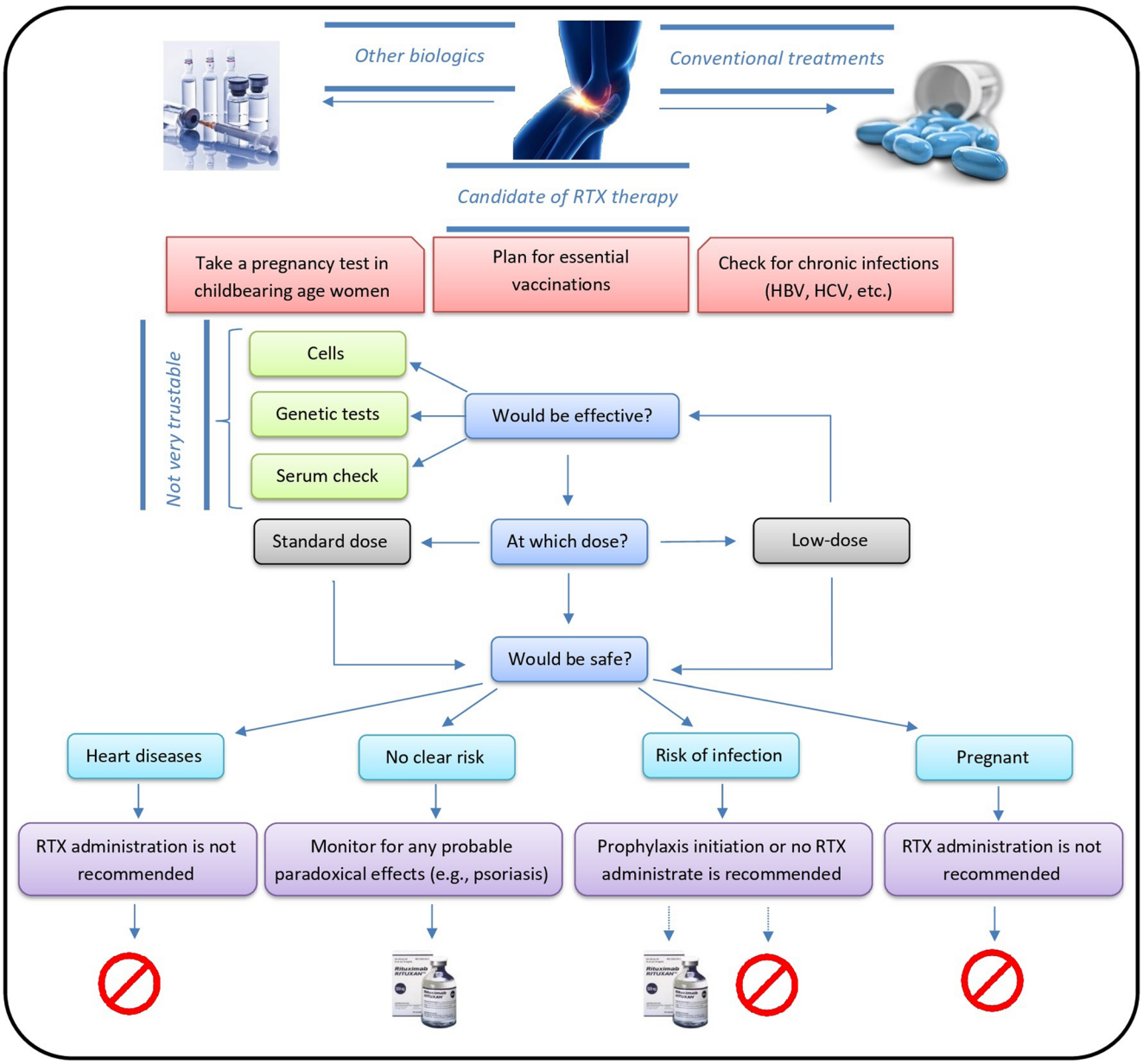

Fig. 2 The recommendation before planning for RTX therapy in RA patients

efficacy, safety, and immunogenicity were reported for PF-05280586, another RTX biosimilar [175].

Conclusion and recommendations

According to the literature review, it could be concluded that RTX is an effective treatment with long-lasting effects on majority of RA patients. Although the superiority of RTX to anti-TNF agents is not very clear, non-responders to TNF blockers have a great chance to achieve remission by RTX therapy. Regarding the optimum doses of RTX, there is no consensus. However, low-dose RTX might be an alternative for standard dose for patients who cannot tolerate or are at the risk of infection development/reactivation. RTX seems a safe treatment for RA patients, while particular attention to those with a chronic infection, such as CHB, is required. Additionally, because of some reported paradoxical reaction, close monitoring of patients is recommended. Essential vaccination also should be administrated before RTX initiation. Prediction of response to RTX therapy is still in its juvenile stages. To date, the different genetic factors, as well as the presence of specific cells or proteins, have been identified as the probable predictor of RTX response. Evaluation of sensitivity and specificity of them before adopting them for use in clinical practice is crucial. In this regard, it could be recommended that the determination of the efficient and safe dose might be related to such predictors or markers, which needs further studies. The lack of studies on safety of RTX exposure before/during the pregnancy has led to concerns regarding RTX safety during conception. Until reaching a consensus, following the last released guidelines are recommended. Figure 2 summarizes these findings and recommendations.

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Compliance with ethical standards

Disclosures None.

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