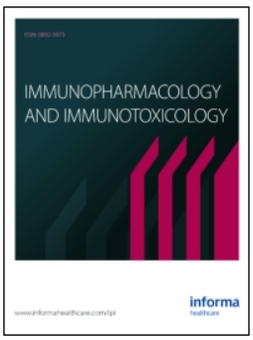

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A systematic review on efficacy, safety, and treatment-durability of low-dose rituximab for the treatment of Pemphigus: special focus on COVID-19 pandemic concerns

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REVIEW ARTICLE

A systematic review on efficacy, safety, and treatment-durability of low-dose rituximab for the treatment of Pemphigus: special focus on COVID-19 pandemic concerns

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ABSTRACT

Background: Rituximab is a FDA-approved monoclonal antibody for adults with moderate to severe potentially life-threatening pemphigus vulgaris. Recent studies have focused on assessments of efficacy and safety of low-dose rituximab (<2 gram in each cycle).

Method: Databases were searched from 2010 to 2020 (last update: 1 June 2020).

Result: Nine studies were entered; including180 cases (92: women, 88: men, age range: 9–83 years). The dosages of each Rituximab cycle varied between ultra-low-dose (≤500 mg for a cycle, either multiple infusions or a single infusion), low-dose (2×375 mg/m^2 or 2×500 mg) and modified-dose (3×375 mg/m^2 or 3×500 mg). The efficacy and safety of Rituximab in the studies are known by the recovery time, relapse time, and side events. According to the studies, 2×500 can lead to complete remission in a broad range, from 35 to 82%. These differences might be explained by different endpoints and variable cumulative corticosteroid dosage after RTX administration. Although the studies showed that low dose RTX is efficient, there are some controversies regarding the choosing low-dose for severe patients.

Conclusion: Considering the effectiveness of low-dose, intermediate dose, and ultra-low-dose protocols of Rituximab in inducing remission in pemphigus disease and considering factors such as cost of therapy, and the need to induce a minimum of immunosuppression for a minimum duration in the COVID-19 pandemic, suggested to use low-dose Rituximab protocol (2 infusions of 500 mg Rituximab: interval of 2 weeks) to induce the remission in mild-to-moderate pemphigus patients.

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Pemphigus; rituximab; low-dose; under-standard dose; ultra-low-dose; autoimmune bullous skin disorder; systematic review; COVID-19

Introduction

Pemphigus is a chronic, rare, and life-threatening autoimmune group of blistering disease that can affect the skin and/or mucous membranes [1]. Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF) are the two most common subtypes of pemphigus; the development of the former causes blisters on the skin and mucous membranes, while the latter only affects the skin [1]. In the meantime, there are several things in common regarding the pathogenesis and their treatments. Systemic corticosteroids alone or in combination with corticosteroid-sparing agents such as azathioprine or mycophenolate mofetil are usually being considered as the first-line treatments for this disease, although recently targeted therapies, such as rituximab (RTX) are changing the rules of the game [1]. Conventional treatments are associated with serious side effects, mainly infections. Thus, the main problems are adverse effects and complications of long-term corticosteroids and immunosuppressive agents [1]. Recently, the treatments of these autoimmune diseases are shifting from these conventional therapies to more targeted therapies [2]. RTX is a monoclonal antibody directed against the CD20 molecule on most of the B lymphocytes has been approved by the US FDA for adult patients with moderate to severe PV (FDA Reference ID: 427429). First, it has been used with promising results in the treatment of severe, recalcitrant, or relapsing pemphigus [3]. However, during the last few years, it is being considered as the first-line treatment, even for new patients, along with a short-term prednisone therapy to have better disease control [4]. RTX-containing regimens for pemphigus patients increase the chance of achieving a complete remission (CR) off-therapy outcome, almost three times higher than the corticosteroid-alone

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Supplemental data for this article can be accessed here.

regimen [4,5]. Furthermore, we showed that patients under early treatment with RTX (≤6 months) may not only have a higher chance to experience a CR but also could enter the remission phase significantly faster than those who started RTX years after disease diagnosis. In the meantime, the time of remission off corticosteroids was significantly longer [6]. In addition to all of these clinical advantages, the dermatology life quality index and skindex scores were significantly better in patients treated with RTX [4,7]. Regarding the safety issues, many studies have shown the favorable safety profile of RTX in the management of pemphigus patients [8–11]. Nowadays, there are two commonly used protocols for pemphigus therapy: the lymphoma treatment protocol (375 mg/m^2 each week for 4 weeks) and rheumatoid arthritis (RA) protocol (two infusions of 1000 mg, administered 2 weeks apart), although multiple other protocols with the lower cumulative dose of RTX had been successfully used. However, there is no consensus on optimum dosing protocol. The concerns about the risk of infections, infusion reactions, and relative contraindications in cardiopulmonary patients, and also the high cost of this medication often limit the clinical utility of the full dose drug. RTX at the dose of less than 1 mg/m2 in healthy individuals could entirely deplete peripheral B cells; it seems that lower dosages of RTX might be effective for pemphigus patients [12]. RTX may have some adverse effects including severe infections, immediate infusion-related such as allergic responses, immediate cardiac effects, and pulmonary embolism [8]. However, using low-dose (500 mg at 2 weeks interval) or ultra-low-dose (≤500 mg) RTX may help to have a better side effect profile. Thus, some studies focused on lower-dosage of RTX to assess effectiveness in patients with pemphigus [7,13–19]. Furthermore, the outbreak of coronavirus disease 2019 (COVID-19) affects the management of several cutaneous immune-mediated chronic diseases.

Here, we have conducted a systematic review as there is ongoing controversy over the most appropriate dose, to evaluate the clinical and immunological outcomes of lower doses of RTX to provide an overview of the efficacy and safety of the drug in patients suffering from pemphigus.

Materials and methods

Search strategy

A systematic literature search was conducted for all published articles associated with RTX therapy in pemphigus but limited to the studies that had used low-dose, which could ultra-low-dose (≤500 mg for a cycle, either multiple infusions or a single infusion), low-dose (2×375 mg/m^2 or 2×500 mg), modified-dose (3×375 mg/m^2 or 3×500 mg). Medline/PubMed and Embase databases were searched using predefined keywords (Supplementary 1) from 2010 to 2020. The last search update was performed on 1 June 2020. Additionally, the references of the selected articles were checked for any probably missed articles.

Selection criteria

Among the studies that appeared based on the employed keywords, any types of study published in English with original data, including interventional studies that reported using RTX for pemphigus patients that met the inclusion criteria were considered. The inclusion criteria are as below:

1. Patients must have a diagnosis of pemphigus, based on clinical manifestation along with direct immunofluorescence (DIF) and/or antibodies in the serum against the desmoglein (Dsg)1/3.
2. Patients should be treated with the RTX at rheumatoid arthritis protocol (a dosage lower than the standard dose (2000 mg).) and lymphoma protocol (375 mg/m^2 each week for 4 weeks).

Studies that do not contain any original data, such as review articles had been excluded, although they were searched for probable missing reports and studies.

Data extraction

After the selection of target studies, based on the full-text, data extraction was performed from each article by two authors, independently. The extractors had carefully reviewed and categorized demographic data, treatment protocol, outcomes, and probable follow-up periods finally, all the data were rechecked and compared; any inconsistencies were resolved by referring to the full text of the articles until reaching a consensus.

Outcomes

The outcomes of this study include efficacy (either complete remission, CR or partial remission, PR), disease-free duration, therapeutic sustainability, achieving negative DIF or ELISA, reduced need to systemic corticosteroids or adjuvant immunosuppressive drugs), reduced recurrence and relapse and safety (we consider as experience any treatment-related side effects) of low/under optimal doses of RTX for treatment of Pemphigus.

Results

Search results

Searching in databases has led to finding 1025 records, of which 184 were duplicates. Additionally, 47 studies have been ignored since they were written in the non-English language. Among the 794 remaining articles, which were evaluated based on titles and abstracts. We excluded 736 articles, due to using standard dose ($n = 162$), irrelevant studies ($n = 483$), case reports ($n = 91$). Finally, 58 articles had been selected for full-text evaluation. Among them, 9 were selected to be discussed and 49 were excluded due to insufficient/irrelevant data. Figure 1 illustrates the selection procedure of the studies in PRISMA Flow Diagram.

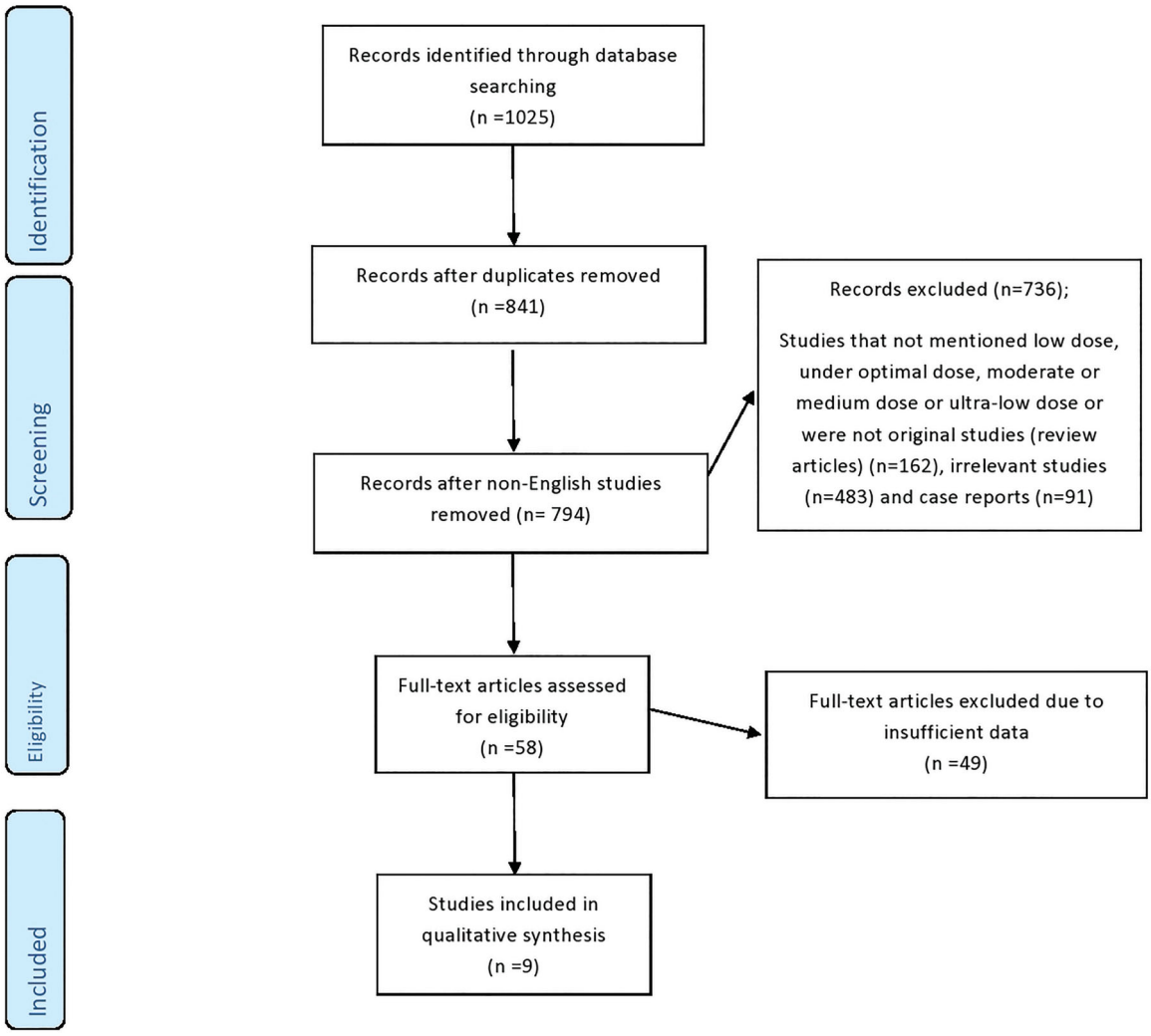

Figure 1. PRISMA 2009 flow diagram.

Studies' characteristics

In total, we have included one randomized controlled trial (22 patients) and eight cohort/case series (158 patients). In total, 88 men and 92 women, who their ages vary in a range of 9–83 years old, have been included. Regarding the disease subtype, 150 had PV, 30 had PF. The dosages of each RTX infusions were different, including ultra-low-dose (4×100 mg, single infusions of 200 mg, or 250 mg), low-dose (2×375 mg/m^2 or 2×500 mg), as well as modified dose (3×375 mg/m^2 or 3×500 mg).

Studies' description and characteristics

The story of low-dose RTX has started in 2011, which Horvath et al. [16] hypothesized that a lower dose of RTX (less than 4×375 mg/m^{2}or 2×1000 mg) might be sufficient for pemphigus. In fact, based on the capability of RTX in depletion B cells by a single dose as low as 100 mg/m2 in lymphoma patients [20], for the first time, they evaluated the outcomes of low-dose RTX (2×500 mg rituximab with 2 weeks intervals) in pemphigus patients. They designed prospective, nonrandomized, and treated 15 pemphigus patients. In addition to the setting clinical endpoints, sera autoantibodies and CD20+ B cells were evaluated through ELISA and flow cytometry, respectively.

In the same year, another study conducted by Kim et al. [21] but with a retrospective design has been published; it contains 27 patients and tried to compare the clinical efficacy of different doses of RTX. More precisely, patients were categorized, 12 and 15 patients have received two or more than two infusions, respectively; each 375 mg/m^2 ($n = 12$: 2×375 at 1 week interval vs. $n = 15$: 3 or more $\times$ 375 at 1 week interval). Patients had been followed for at least 6 months

Two years later, Cho et al. [22] conducted a retrospective design study with 23 included patients. Two groups have been defined based on the severity. Those in the more severe group received three ($n = 2$) or four ($n = 8$) infusions of RTX at the dosage of 375 mg/m^2 body surface area at 1-week intervals and the other group was treated with two infusions ($n = 13$) of the same dose given 1 week apart. The mean follow-up was 25.6 and 17.8 months for each group, respectively. Based on that study, B cells in all, except two patients in the severe group have been depleted. Also, the mean times to reach disease control were 5.6 and 3.9 weeks in more severe and less severe groups, respectively. This

study showed that at least in mild to moderate pemphigus, two infusions of RTX are sufficient and safe to control the disease activity.

In 2013, another study with 2 patients was conducted that Chay et al. [23] evaluated retrospectively the off-label use of low-dose RTX (500 mg twice as a single course 1–2 weeks apart) at two academic centers, from mid-2008 until the end of 2011.

In the next year in 2014, another pilot study with the prospective, randomized, observer-blinded, parallel-group design, by Kanwar et al. [7] had compared the clinical efficacy between treatment with 2×500 mg RTX vs. 2×1000 mg RTX with a 15-day interval 22 patients with pemphigus (11 patients in each arm). All patients were followed up for 48 weeks with regular visits up to week 40.

In another article published in 2014, Londhe et al. [24] reported the results of a historical cohort on 24 patients with refractory pemphigus (23 PV and one PF). Data of 14 men and 10 women with mean disease duration of 33 months before RTX therapy were evaluated. The patients were treated with infusions as three weekly consecutive doses of 375 mg/m^2 of RTX and one similar dose repeated after 3 months of third dose, with or without many concomitant immunosuppressive drugs.

Three years later, in 2017 Robinson et al. [15] performed a long-term retrospective review of 9 pemphigus patients who were given the two infusions of 500 mg, two weeks apart.

In another study conducted in 2017 by Gupta et al. [17] was a prospective open-label study on 50 patients with pemphigus (9 PF and 41 PV), the mean age of patients was 35.7 years. Two doses of 500 mg RTX at 15 days interval were used.

Although this is not the last article in the story of RTX, and this trend will continue in the years to come, the last article published in 2020 by Russo et al. [14], a prospective nonrandomized open-label case series as a pilot study including eight PV patients (5 men and 3 women). Patients were treated with an ultra-low dosage of RTX (<500 mg). Once patients were under treatment with oral prednisone (0.3–0.5 mg/kg/daily), a single infusion of 200 mg RTX was initiated, and oral prednisone has been rapidly tapered. Length of follow-up was 18–101 weeks (mean of 52 weeks). An ultra-low dosage of RTX could be considered as first-line therapy for pemphigus to probably minimize the side effects and cost of the long-term immunosuppressive regimens.

In Table 1, we summarized the characteristics and design of 9 studies we inserted in this systematic review.

Efficacy

In Table 2, the results of nine studies about the efficacy of low-dose RTX for the treatment of pemphigus are shown; studies have been ordered based on publication date.

The first study was a prospective nonrandomized, single-center open case series that conducted by Horváth et al. [16] The end-point of the study was time to reach CR. Eight patients from 15 achieved CR in a median period of 51 weeks and seven patients achieved partial remission in a median period of 34.5 weeks by 2×500 mg rituximab with 2 weeks intervals regime. Exposure to RTX led to dropped of CD20+ B cells to undetectable (<1%) levels in all patients, although the anti-Dsg1/3 levels were detectable in some patients. All the patients were relapse-free during the first year; 40% relapsed during the second year with a median of 97 weeks after RTX treatment.

In the second study, a retrospective case series conducted by Kim et al. [21] ($n = 12$: 2×375 at 1 week interval vs. $n = 15$ received 3 or more $\times$ 375 at 1 week interval). The endpoints of the study were time to disease control, (PR) or (CR). Although those who received more than two infusions had reached complete remission earlier (443 vs. 149 days, $p = .06$), there was no significant difference between the numbers of patients who reached partial remission (147 vs. 135 days, $p = .65$). Despite the occurrence of disease relapse was 67% after a median of 11.5 months follow-up in the two infusion groups, no relapse occurred in the next group, which suggests benefiting of patients from higher cumulative dose in a cycle.

In third study that conducted by Cho et al. [22] the improvement of disease was assessed based on the pemphigus severity score ($n = 10$ severe pemphigus: 3–4 $\times$ 375 mg/m^2 rituximab at 1-week intervals vs. $n = 13$ mild to moderate pemphigus:2 $\times$ 375 mg/m^2 rituximab at 1-week intervals). As the results, in more severe patients who received a higher dose, six patients (60.0%) achieved CR, including two patients off therapy (CR OFF) and four patients on therapy (CR ON). The other four patients (40.0%) achieved PR on therapy (PR ON). In the other group, nine patients (69.2%) achieved CR (4 CR off-therapy, 5 CR on-therapy) and four patients (30.8%) achieved PR on-therapy. It is worthy to note that no significant difference between the two groups with different severity might suggest the effectiveness of higher dose in more severe cases.

In the retrospective case series that conducted by Chay et al. [23] (2×500 mg at 1–2 weeks interval) CR were observed in 16 (35%), PR were observed in 19 (41%) and 11 (24%) patients was no response to rituximab. Authors of this study said that rituximab can be used off-label to treat several severe and/or refractory life-threatening immunological disorders with a reasonable safety profile in 76% of patients.

In 2014, a case series was conducted by Londhe et al. [24] the main clinical outcome was considered as healing of cutaneous and mucosal lesions and pemphigus activity score (PAS) was used for improvement assessment, which was recorded after 6 months of the third dose of RTX. Mean PAS was 5.58 at baseline which significantly decreased to 2.04, 6 months after the third dose ($p < .001$). Five patients showed PR and 19 showed CR 3 months after starting RTX. the authors found that pemphigus patients who received a modified lymphoma protocol (defined as intermediate-dose RTX) comprising three consecutive weeks of 375 mg/m^2 and a fourth infusion are given 3 months after the third infusion could experience complete remission about 79 and 21% partial response with two relapses after the initial remission (3×375 mg/m^2 at 1 week interval, one similar dose repeated after 3 months).

Table 1. Characteristics and design of studies.

First author	Type of study	Demographic characteristic	Regimen and dosage of Rituximab
Horvath (2011)	Prospective nonrandomized, single-center open case series	Total: $n = 15$, 3 PF and 12 PV 10 men, 5 women. Mean age > 50 years. Median disease duration: 5 years (2–12)	2 × 500 mg & 2 weeks intervals. Most of them had comedication of systemic non-biologic immunosuppressive therapy
J.H. Kim (2011)	Retrospective case series	Total: $n = 27$ Arm1: 12 with 7male, 5 females, Arm2: 15 with 7male, 8females 25 PV and 2 PF Mean age: 48 years	$n = 12$: 2 × 375 mg & 1 week interval VS $n = 15$: 3 or more × 375 & 1 week interval.
H.H. Cho (2013)	Retrospective case series	Total: $n = 23$ 16 PV, 7 PF 10 man, 13women Mean age > 50 years Age range: 31–80	$n = 10$: Severe pemphigus: 3–4 × 375 mg & 1 week intervals VS $n = 13$: Mild to moderate pemphigus:2 × 375 mg & 1 week intervals
J. Chay (2013)	Retrospective case series	Total: $n = 2$ PV 2 women 34 & 45 years old.	2 × 500 mg & 1–2 weeks interval
Pradnya J. Londhe (2014)	Case series, historical cohort:	Total: $n = 24$, 23 PV and 1 PF 14 Men, 10 women, Mean disease duration: 33 months	3 × 375 mg & 1 week interval One similar dose repeated after 3 months of third dose
A.J. Kanwar (2014)	RCT	Total: $n = 22$ Each arm: $n = 11$ 11man, 11women 15PV, 7PF Mean age: 33 years	Low-dose: 2 × 500 mg & 15 days interval VS High-dose: 2 × 1000 mg & 15 days interval
Jaya Gupta (2017)	Prospective open case series	Total: $n = 50$ 9 PF, 41 PV Mean age: 35.7 years 30 Females, 20 males Mean of disease duration: 1.5 years	2 × 500 mg & 15 days interval
Aaron J Robinson (2017)	Case series, historical cohort	Total: $n = 9$ 8 PV, 1 PF Mean age > 50 years 5 Women, 4 men.	2 × 500 mg & 2 weeks interval With concurrent adjuvant therapy
Irene Russo (2020)	Prospective non-randomized open case series	Total: $n = 8$ PV 5 Males, 3 females Aged 34–73 years Disease duration range: 2–7	Ultra-low dosage of rituximab: a single infusion of 200 mg.

In the same year, Kanwar et al. [7] conducted the RCT. There was no statistically significant difference between the groups: 2 × 500 mg rituximab at 15 days interval vs. 2 × 1000 mg rituximab at 15 days interval in terms of either early endpoints (time to disease control and time to complete consolidation phase) or late endpoints (reaching PR or CR) and cumulative dose of corticosteroids. Although both groups significantly improved, a slightly higher decrease in disease severity and decline in serological autoantibodies were noted in the higher dose group at week 40. Relapse was reported as 36 and 64% of patients in standard and low-dose groups, while the difference in terms of rate and time to relapse were not statistically significant. The total cumulative dose of corticosteroids was also comparable. Despite the complete depletion of peripheral B cells in both groups, it was reported that low-dose RTX is associated with earlier B cell repopulation (by eight weeks).

In the prospective open study of Gupta et al. [17] Forty-one (82%) of 50 patients had a CR either on or off treatment, and 9 (18%) patients showed PR at the end of 3rd month with 2 × 500 mg rituximab at 15 days interval regime. After 6 months, 40% maintained off CR and 38% were continuing with steroids with or without immunosuppressants. Except for two patients in each group who showed a disease relapse, others were in remission, successfully managed with extra doses of RTX. The baseline PAS was 7.98, which reduced to 1.24, 3 months after the second dose. All patients achieved remission within 52 weeks after treatment. The median of anti-Dsg3 antibody levels in PV patients significantly reduced from 160 at baseline to 4.2 at the end of the follow-up period. 12 of 19 patients after complete remission, did not need any other systemic therapies while 7 patients continued systemic immunosuppressives (no or low-dose of steroids plus adjuvant immunosuppressants). Two patients relapsed after initial improvement; one received a moderate dose of oral steroids plus immunosuppressant and the other was received a single dose of RTX. After 6 months, the majority of patients showed antibody levels in the negative range except for three patients whose anti-Dsg3 levels remained positive. The mean follow-up duration was about 7-24 months and the authors found the intermediate dose of RTX can induce a prolonged clinical remission in pemphigus patients after a single course of four infusions but in a different model compared with the classic standard 4 weekly infusion protocol. They concluded that RTX can induce a prolonged remission after a course of modified lymphoma protocol or intermediate-dose protocol.

Table 2. The results of studies about the efficacy of low-dose RTX for the treatment of pemphigus.

First author	Regimen and dosage of rituximab	Efficacy of treatment	Conclusion
B. Horvath (2011)	2 × 500 mg & 2 weeks intervals	CR:53.33% Median period: 51 w PR: 46.66% Median period: 34.5 w Relapses: 40% Median: 97 w after start of therapy B-cell numbers <1% after first infusion	A low dose of rituximab is an effective and safe treatment for pemphigus. Relapses may occur, mostly at the end of the second year.
J.H. Kim (2011)	$n = 12$: 2 × 375mg & 1 week interval VS $n = 15$: 3 or more × 375 & 1 week interval.	Time to achieve PR: no significant difference (147 vs. 135 days, p=.65) Time to achieve CR: group 2 better outcomes than group 1 (443 vs. 149 days, p=.06) Relapse rate: group 2 better outcomes than group 1 (0 vs. 67%, p<.01).	Three or more infusions of rituximab are more effective than two infusions for the treatment of pemphigus
H.H. Cho (2013)	$n = 10$: severe pemphigus: 3–4 × 375 mg & 1-week intervals VS $n = 13$: mild to moderate pemphigus:2 × 375 mg & 1-week intervals	Group 1; CR: 60.0% CR OFF: $n = 2$, CR ON: $n = 4$ PR ON: 40.0% Relapse: $n = 5$ Group 2; CR: 69.2% CR OFF: $n = 4$, CR ON: $n = 5$ PR ON: 30.8% Relapse: $n = 3$	Rituximab is an effective and safe treatment method in severe, recalcitrant pemphigus and in mild to moderate pemphigus. Low dose of rituximab seemed to be sufficient to treat mild to moderate pemphigus.
J. Chay (2013)	2 × 500 mg & 1–2 weeks interval	CR: $n = 16$ (35%) PR: $n = 19$ (41%) No response: $n = 11$ (24%)	Rituximab can be used life-threatening immunological disorders with a reasonable safety profile in 76% of patients.
J. Londhe (2014)	3 × 375 mg & 1 week interval One similar dose repeated after 3 months of third dose	Mean PAS was 5.58 at baseline falling to 2.04, 6 months after the third dose (p<.001). PR: $n = 5$ CR: $n = 19$ 3 Months after starting rituximab. Relapse: $n = 2$ The median of anti-Dsg3 antibody levels in PV patients reduced from 160 at baseline to 4.2 at the end of follow-up period (p=.001).	Intermediate dose of rituximab is able to induce a prolonged clinical remission in pemphigus after a single course of four infusions
A.J. Kanwar (2014)	2 × 500 mg & 15 days interval VS 2 × 1000 mg & 15 days interval	Fall in severity score was significantly more in arm2 than 1 (p=.049). Higher relapse rate and shorter time to relapse were seen in arm1. Dsg1 and Dsg3 significant decline in arm2.	Clinical and immunological parameters suggest improved outcomes in patients receiving high-dose (2 × 1000 mg) rituximab
Gupta (2017)	2 × 500 mg & 15 days interval	The mean pretreatment pemphigus activity score was 7.98, which reduced to 1.24, 3 months after the second dose 82% CR after 3 months 18% PR after 3 months 40% CR After 6 months 38% PR After 6 months 4% had a relapse	Low-dose rituximab can induce a prolonged clinical remission in pemphigus with minimal side effects.
Robinson (2017)	2 × 500-mg & 2 weeks interval	B-cell depletion in all patients Three of these patients required repeat dosing cycles due to either relapsed disease or incomplete disease control	Low-dose rituximab is safe and effective, and re-dosing in the event of relapse is an efficient means of achieving ongoing disease control.
Irene Russo (2020)	A single infusion of 200 mg.	All patients had a positive response after infusion. 5 CR 3 PR	An ultra-low dosage of rituximab could be an effective treatment for pemphigus vulgaris.

In the case series that conducted by Robinson et al. [15] (2 × 500 mg at 14 days interval) Significant B-cell depletion was observed in all the patients and they concluded that low-dose RTX with concurrent use of adjuvant immunosuppressive is effective for pemphigus control but close serological and B-cell monitoring is suggested in these patients to identify patients at higher relapse risk for re-dosing or increasing the adjuvants. The clinical response to RTX had a wide inter-individual variation. Three out of nine patients relapsed and needed additional cycles of RTX for disease control. Interestingly for all relapsed patients, B-cell repopulation and serological evidence of relapse were observed before the clinical relapse.

In the last study that was a prospective non-randomized open case series by Russo et al. [14], (A single infusion of 200 mg) At the end of the follow-up period, 5 patients achieved CR, and 3 achieved PR.

Table 3. safety profile and adverse effects of RTX.

First author	Regimen and dosage of rituximab	Probable side effects in each arm
B. Horvath (2011)	2 × 500 mg & 2 intervals	(4/15):26% Mild, early adverse effects; Influenza-like symptoms:2, Mild herpes zoster:1, Atrioventricular nodal reentry tachycardia with chest pain (he had arrhythmias in his medical history):1
J.H. Kim (2011)	$n = 12$: 2 × 375 mg & 1 week interval VS $n = 15$: 3 or more × 375 & 1 week interval.	No severe adverse effect
H.H. Cho (2013)	$n = 10$: severe pemphigus: 3–4 × 375 mg & 1-week intervals VS $n = 13$: mild to moderate pemphigus:2 × 375 mg & 1-week intervals	Experienced mild, transient fever and tachycardia during rituximab infusion:1
J. Chay (2013)	2 × 500 mg & 1–2 weeks interval	Significant adverse event related to infectious complications: 50% Death: 25% Allergic/infusion reactions: 25%
Pradnya J. Londhe (2014)	3 × 375 mg & 1 week interval One similar dose repeated after 3 months of third dose	Moderate and brief fever and chills ($n = 6$) Hypotension ($n = 2$, 8%) Hypertension ($n = 1$, 4%) Herpes zoster ($n = 2$, 8%) Extensive tinea corporis ($n = 1$, 4%) Pulmonary embolism in diabetic patient ($n = 1$, 4%) Recurrent diarrhea with weight loss of 10 kg within a month ($n = 1$, 4%)
A.J. Kanwar (2014)	2 × 500 mg & 15 days interval VS 2 × 1000 mg & 15 days interval	Mild infusion reactions Upper respiratory tract infections Diarrhea Striae and acneiform eruptions
Jaya Gupta (2017)	2 × 500 mg & 15 days interval	Chills ($n = 1$) Urticaria ($n = 1$) Hypotension ($n = 1$) Herpes zoster ($n = 1$)
Aaron J Robinson (2017)	2 × 500 mg & 2 weeks interval	Minor infections ($n = 6$)
Irene Russo (2020)	A single infusion of 200 mg.	Sepsis due to Citrobacerfreundii and a pneumonia due to Haemophilus influenzae ($n = 1$)

Safety

In Table 3, we focused on the safety profile and adverse effects of RTX based on the original-clinical studies we included.

In the study that used a single course of two infusions of 500 mg of rituximab was administered with an interval of 2 weeks [16], in four patients (26%) early mild adverse effects were seen; two of them involve influenza-like symptoms, one of them had a mild herpes zoster and the fourth one who had arrhythmias in his medical history, shown an atrioventricular nodal reentry tachycardia with chest pain. At week 29, a serious adverse event seen followed by mycophenolate mofetil 2 g daily in a patient; sepsis due to neutropenia. After stopping mycophenolate mofetil the patient recovered from the neutropenia and his disease improved.

In the Retrospective case series that patient divided into two groups. Group 1 received two infusions of rituximab, and group 2 received three or more infusions at 1 week interval [21], RTX treatment was well tolerated in all patients without any adverse effects. One patient died 3 months study because of gastric perforation which may not have been related to rituximab.

In another case series that conducted two years later [22], patients were also divided into two severe and moderate groups, a patient experienced transient mild fever and tachycardia during RTX infusion. So RTX was infused at a slower rate and the symptom disappeared.

In the study conducted by Chay et al. [23] a low-dose of RTX (500 mg twice, given 1–2 weeks apart) was used. In eight patient significant adverse events was seen, 50% was infectious complications, 25% death and 25% infusion allergic reactions.

In the study that three weekly consecutive doses of 375 mg/m^2 of RTX and one similar dose repeated after 3 months of the third dose was used [24], the most of Side effects occurred during the first infusions; moderate fever and chills (6/24), hypotension (2/24), and hypertension (2/24) which were controlled by either stopping or decreasing the rate of infusion, was seen. In second infusions, patients experienced no infusion reactions. 8% of patients (2/24) developed herpes zoster and the next infusion was deferred till the lesions healed after treatment with an antiviral drug. One of them also developed an extensive tinea corporis. And, a diabetic patient developed a carbuncle that was treated with antibiotics, after that he involved to pulmonary embolism (a month following the first three infusions) and was treated successfully in an ICU setting. One patient developed recurrent diarrhea with weight loss of 10 kg within a month and was diagnosed with Isospora diarrhea that was treated successfully with cotrimoxazole.

In the study that low-dose RTX (doses of 500 mg rituximab 15 days apart) was used [7], Six of 22 patients developed minor infections during the course of their treatment; like upper respiratory tract infections, diarrhea, striae and

Table 4. Relapse and remission time.

First author	Regimen and dosage of rituximab	Follow-up duration and results of each arm, relapse rate (RR)
B. Horvath (2011)	2 × 500 mg & 2 weeks intervals	Median: 94 w Range: 32–152 w
J.H. Kim (2011)	$n = 12$: 2 × 375 mg & 1 week interval VS $n = 15$: 3 or more × 375 & 1 interval.	Group 1: Mean: 11.5 m Group 2: Mean: 18 m
H.H. Cho (2013)	$n = 10$: Severe pemphigus: 3–4 × 375 mg & 1-week intervals VS $n = 13$: mild to moderate pemphigus:2 × 375 mg & 1-week intervals	Group 1: Mean: 25.6 m Group 2: Mean: 17.8 m
J. Chay (2013)	2 × 500 mg & 1–2 weeks interval	Variable
Pradnya J. Londhe (2014)	3 × 375 mg & 1 week interval One similar dose repeated after 3 months of third dose	Range: 7–24 m
A.J. Kanwar (2014)	2 × 500 mg & 15 days interval VS 2 × 1000 mg & 15 days interval	Mean: 12 m
Jaya Gupta (2017)	2 × 500 mg & 15 days interval	Median: 17 m. Range: 12–25 m
Aaron J Robinson (2017)	2 × 500 mg & 2 weeks interval	Variable
Irene Russo (2020)	A single infusion of 200 mg.	Mean: 52 w Range: 18–101 w

acneiform eruptions were seen in both groups without any significant difference. But no major complications were observed.

In the study that conducted in 2017 [17], and low-dose RTX (doses of 500 mg rituximab 15 days apart) was used, in one case chills and in one case urticaria following infusion was seen, one had hypotension and one developed herpes zoster which was managed without any complication.

In the second study that conducted in 2017 [15], and 500-mg doses of RTX separated by 14 days along with concurrent adjuvant therapy was used, six patients (37.5%) developed minor infections during the course of their treatment, but no major complications were observed.

In the last study [14], that a single RTX infusion of 200 mg was used, one case with sepsis and one pneumonia was reported.

It should be notified that various doses of prednisolone in about all studies or different immunomodulators in some studies when it was necessary have been used in practice during these clinical studies.

We focused on the relapse and remission time in Table 4 based on studies' follow-up. In Table 5 The efficacy and safety reported by studies that compared high-dose (more than two 500 mg) with low-dose (two infusions of 500 mg) of RTX.

Discussion

RTX, a chimeric anti-CD20 monoclonal antibody is considered the first-line therapy for moderate to severe pemphigus. Although RTX is considered the first-line therapy for pemphigus, there is yet a lack of consensus on the optimum dosage and schedule of its infusion in this disease [1,25]. Different infusion protocols have been used including high-dose (either lymphoma protocol or RA protocol), intermediate-dose, low-dose, and ultra-low-dose protocols [12]. In this study, systematically, we showed that low-dose RTX could be as efficient and standard dose. Additionally, it seems that using lower cumulative RTX might help to decrease the rate of side-effects.

Three studies (two retrospective case series and one randomized clinical trial) out of 11 studies compared the standard dose of RTX (2 infusions of 1000 mg) with low-dose of RTX (2 infusions of 500 mg) have been compared and shown in Table 5 [7,21,22]. Kim et al. compared patients who received two infusions of RTX with those who received three or more infusions. They found that though time to achieve PR in the two groups was a similar time to complete remission and relapse rates were significantly lower in the group with three to more infusions [21]. Cho et al. [22] compared a group of 10 severe pemphigus patients who were treated with three or four infusions of RTX at a dose of 375 mg/m^2 at weekly intervals with a group of 13 mild to moderate pemphigus patients who received two infusions of RTX at the same dose both groups achieved near 60% of complete remission and they suggested that low-dose RTX seemed sufficient to treat mild to moderate pemphigus. In an RCT performed by Kanwar et al. [7]. The efficacy of a high dose (2 infusions of 1000 mg) with a low-dose (2 infusions of 500 mg) of RTX was compared. They found no statistically significant difference between groups in terms of early and late clinical endpoints and cumulative dose of corticosteroids, but relapse rate, adjuvant requirement, and immunological markers (fall in desmoglein antibody levels and CD-19 repopulation) were significantly better in high dose group compared to the low-dose group.

From these three studies that compared the high dose of RTX with the low-dose, it can be inferred that though high-dose protocol displays better outcomes especially in complete remission, relapse rate, adjuvant requirement, and immunological markers the low-dose protocol is sufficient in early disease control as the high dose. Of note, both high and low-dose protocols were well tolerated and similar in terms of adverse effects.

A systematic review and meta-analysis of RTX different regimens for pemphigus Vulgaris by Wang et al. [26] in 2015, authors evaluated data of 578 patients with pemphigus Vulgaris from 30 studies for comparing high-dose (near or $\geq$2,000 mg/cycle) vs. low-dose ($=<$1,500 mg/cycle) RTX. They found no significant difference between the high-dose and low-dose groups in complete remission (CR), time to disease

Table 5. The efficacy and safety reported by studies that compared high-dose (more than two 500 mg) with low-dose (two infusions of 500 mg) of RTX.

Author/year	Study type	Comparison groups	Outcome	Adverse reactions	Conclusion
J.H. Kim/2011	Retrospective case series ($n = 27$)	$n = 12$: 2 × 375 at 1 week interval VS $n = 15$: 3 or more × 375 at 1 week interval.	Time to achieve PR: no difference (147 vs. 135 days, p=.65) Time to achieve CR: group 2 better than group1 (443 vs. 149 days, p=.06), relapse rate: group 2 better than group1 (0 vs. 67%, p<.01).	No severe adverse effect	3 or more infusions of rituximab are more effective than two infusions for the treatment of pemphigus
H.H. Cho/2013	Retrospective case series ($n = 23$)	$n = 10$ Severe pemphigus: 3–4 × 375 mg/m^2 at 1-week intervals. VS $n = 13$ Mild to moderate pemphigus: 2 × 375 mg/m^2 at 1-week intervals.	In group 1; (6/10) 60.0%: CR, 2 CR OFF 4 CR ON 40.0%: PR ON In group 2: (9/13) 69.2%: CR 4 CR OFF 5 CR ON (4/13) 30.8%: PR ON Relapse: 5 in group1, 3 in group 2.	Mild, transient fever and tachycardia ($n = 1$)	Low dose of rituximab seemed to be sufficient to treat mild to moderate pemphigus.
A.J. Kanwar/2014	RCT ($n = 22$)	2 × 500 mg at 15days interval VS 2 × 1000 mg at 15 days interval	The fall in Ikeda severity score was significantly more in high group than in low dose group (p=.049). Higher relapse rate and shorter time to: low-dose rituximab group. Dsg1 and Dsg3 showed a statistically significant decline in the high dose group only B cell repopulation occurred earlier in low group by 8 weeks.	Mild infusion reactions, upper respiratory tract infections, diarrhea, striae and acneiform eruptions were seen in both groups without any significant difference.	Clinical and immunological parameters suggest improved outcomes in patients receiving high-dose (2 × 1000 mg) rituximab

control (TDC), time to complete remission on therapy (TCRon), and relapse. However, the high-dose group was significantly associated with a longer duration of CR compared with the low-dose group. After one cycle of RTX, 76% of patients achieved complete remission. The remission duration was 14.5 months (mean time = 5.8 months) and a 40% relapse rate. Eighteen patients (3.3%) manifested serious adverse effects. In conclusion, variable RTX treatment is well-tolerated and effective in treating pemphigus, and the rates of serious adverse events were similar between the 2 groups (mean 3.3%). Treating pemphigus patients may render them more vulnerable to worse outcomes in case they develop COVID-19. On the other side, some selective immunosuppressants might help to control the "cytokine storm" associated with worse outcomes of COVID-19 [27]. Regarding the discussed issues, the optimum dosage of RTX therapy during the COVID-19 era seems more challenging because of the irreversible effects of RTX on B-cells and the risk of impairing the reconstitution of B-cell immunity for months there are many concerns for continuing or starting RTX for pemphigus patients during the COVID-19 pandemic. Since the onset of the COVID-19 outbreak many studies mainly expert opinions have been published on treatment considerations for pemphigus patients.

Kasperkiewicz et al. [28] have suggested maintaining immunomodulatory therapies for pemphigus patients because treatment withdrawal may lead to uncontrolled disease activity leading to a higher risk of morbidity and mortality. However, they considered patients with a history of RTX treatment within the last 1 year susceptible to a more severe or prolonged course of COVID-19 infection [28]. Shakshouk et al. suggested postponing RTX infusions to delay patients' peak of immunosuppression during COVID-19 peak [29]. On the other hand, studies that evaluated pemphigus patients on RTX during the outbreak of the COVID-19 found RTX infusions safe because patients actively on RTX during this outbreak had no COVID-related symptoms or any major problem [24,30,31]. Given the need to balance proper pemphigus control with a minimum of immunosuppression to reduce the risks of COVID-19 adverse effects during the COVID-19 pandemics, administering lower doses of RTX (low-dose or ultra-low-dose) seems more reasonable.

There were some studies that we did not include in our main tables due to having non-original/clinical design like Amber et al. [32] study that was a systematic review. We searched the references of all review studies do not miss any relevant articles. There were some data about them as you can see the examples in the following.

In 2014 Amber et al. [32] performed a systematic review of the PubMed/Medline database on the published cases of pemphigus patients treated with a single cycle of RTX with one of the four protocols (RA protocol (1000 mg weekly for 2 weeks), Low-dose RA protocol (500 mg weekly for 2 weeks), Lymphoma protocol (375 mg/m^2 for 4 weeks) or Low-dose lymphoma protocol (375 mg/m^2 for 2 weeks)). Among the 155 pemphigus cases reviewed in this study, an overall complete response of 87% was observed. Comparing the different protocols showed that the low-dose RA protocol demonstrated a significantly worse relapse-free score and a significantly lower complete remission rate (57 vs. 85% in the RA standard protocol, $p = .03$). Also, they found that the standard lymphoma protocol is superior to the other protocols in terms of relapse risk. They suggested not using the low-dose rheumatoid arthritis protocol because of its worse clinical response and relapse-free score and in terms of low-dose RTX, low-dose lymphoma protocol RTX could be more logical but the relapse rate is more comparing with standard lymphoma protocol RTX.

Three studies (Horvath, Chay, Fernandez-Martinez) out of 11 studies were about off-label use of low-dose RTX.

Horvath et al. [16] investigated low-dose RTX (a single course of two 500 mg RTX infusions at an interval of 2 weeks) in a group of 15 pemphigus patients (3 PF and 12 PV) without any control group, eight patients (53.3%) achieved complete remission, seven patients (46.7%) achieved partial remission and the relapse rate was 40% in a median of 97 weeks, also they showed that B-cell numbers dropped to less than 1% in patients in remission

In 2013, Chay et al. [23] evaluated retrospectively the off-label use of low-dose RTX (500 mg twice as a single course 1–2 weeks apart, and 1000 mg given as a single dose or doses lower than this) in 52 patients with different autoimmune neurologic, rheumatologic and dermatologic diseases that were resistant to the classic treatments. Complete response and partial response were observed in 35% and 41% of patients respectively (76% overall response). B-cell levels were measured in 29 patients and complete depletion occurred in 28 patients out of 29. In this study, three patients received low-dose RTX for immunobullous skin disorders that we discussed above. Based on this study, low-dose RTX may lead to a favorable outcome in several autoimmune conditions. Although the majority of patients achieved a partial response, given that most of the patients in this study were resistant to the classic treatments and had a poor prognosis, the low-dose RTX outcome still seemed favorable in their opinion.

A systematic review was written by Fernandez-Martinez et al. [33] in 2015, for assessing off-label uses of low-dose RTX including 51 articles (1049 patients) (4 clinical trials, 10 prospective cohorts, 9 retrospective cohorts, 15 case-series, and 13 case reports), the authors found 30 off-label uses of low-dose RTX for different disorders. The main indications were being kidney transplant (646 patients), immune thrombocytopenia (146 patients), pemphigus (45 patients), and autoimmune hemolytic anemia (43 patients), and the most frequently used dosages were twice 500 mg twice dose given 1–2 weeks apart for the musculoskeletal system, nervous system and skin diseases and 100 mg weekly for 4 weeks in hematological diseases and a single dose of RTX 200 mg (range 35–500 mg) in kidney transplant. The overall response (OR) observed was 80.5% with 67.9% of complete responses (CR). Among the most frequent diseases, the OR and CR were 100 and 66.6% in PMP, 97.7 and 65.1% in AIHA, 82.2 and 81.3% for KT, and 70.5 and 50% in PTI, respectively. No side effects were reported and the relapse rates in the follow-up period were: AIHA [38% in 11.5 months [9–35]], PMP [33% in 17 months [8–37]], and PTI [30.9% in 14 months [3–48]]. This review suggested the low-dose RTX as an effective drug in several off-label diseases although further clinical that needs more trials to assess its efficacy.

Two articles (a biphasic RCT and a narrative review in 2018) out of 11 studies were about ultra-low-dose RTX.

In 2018, in a narrative review published by Alaibac et al. [18] assessed ultra-low-dose RTX in autoimmune blistering skin disorders. In that study, the authors concluded that the B-cell burden in autoimmune blistering skin diseases is much lower than that in lymphoproliferative disorders.

In a biphasic RCT in 2018, Schoergenhofer et al. [12] evaluated single, very low RTX doses in healthy volunteers for testing dosing and bio similarity. Biphasic RCT included (1) Pilot phase (16 patients) and (2) Blinded RCT phase (36 patients). In the pilot trial, RTX transiently depleted CD20+ cells by a mean 68, 74, and 97% immediately after the infusion of 0.1, 0.3, and 1 mg/m^2, respectively. In the randomized trial (second phase), CD20+ cells decreased by a mean $48-55\%$ and 81–87% after infusion of 0.1 or 0.3 mg/m^2 of proposed biosimilar RTX or reference RTX, respectively. In both trials, a total of 106 non-serious, non-severe adverse effects (AEs) were documented. Among them, 56 AEs were graded as moderate and 50 as mild with 33 suspected to be related to the trial drugs. All but two AE were resolved until the final safety visit. All occurring AEs have been described earlier to be associated with RTX exposure. In a recently published trial comparing full dose and half-dose RTX in pemphigus patients with relapse. It is known that several studies have been shown that the higher the concentration of RTX, the better the therapeutic response. The serum concentration of RTX is directly correlated with the RTX dose and frequency of infusions. Repeated RTX infusions lead to the high serum concentration of RTX, because of the ability to capture cells residing in immune privilege sites and the ability to eliminate CD20+ cells that migrated from the bone marrow, spleen, and lymph nodes after the first infusion. Moreover, a single dose of RTX may accelerate B cell recovery, and repeated RTX infusions may delay B cell repopulation. The authors concluded that although overall each regimen has its own benefits it seems that a full dose of RTX is significantly superior and more effective to control the relapsed case of pemphigus compared to half the RTX dose [34].

The authors of this study have been researched on dermatologic disorder considerations and novel therapies in the COVID-19 pandemic especially disorders that needed to be managed by systemic immunomodulators [35–45]. Also the authors conducted a cohort study about characteristics and

outcomes of COVID-19 in patients with autoimmune bullous diseases that showed a higher risk of infection with COVID-19 virus in this group of patients also higher risk of hospitalization especially in patients that were taken the prednisolone in doses of greater than 10 mg/d and what was really important was the each passing month from the last dose of RTX decreased the risks of infection or hospitalization. Therefore, patients on long-term and higher doses of prednisolone and recent RTX therapy should be monitored more closely and RTX administration needs paying more attention for better decision making which confirms and enhances the necessity of this systematic review for the recommendations about these patients [46–54]. It should be notified that, now, the authors of this study have been conducted 2 RCTS with mainstay of use of low dose RTX in practice for management of pemphigus vulgaris.

Limitations

All studies have limitations. This study also had its limitations. These limitations include the following:

- The studies studied were limited to English language studies.
- Case series and case report studies were excluded from the study.
- The databases were searched between 2010 and 2020 and study before 2010 were excluded.

Conclusion

Due to the limited number of articles included in this systematic review as well as the results of the articles submitted, it is not possible to reach a definitive conclusion. But in summary, considering the effectiveness of RTX's protocols in inducing remission in pemphigus disease, the cost of therapy, and the need to induce a minimum of immunosuppression for a minimum duration in the COVID-19 pandemic, we suggest using low-dose RTX protocol (2 infusions of 500 mg RTX at an interval of 2 weeks) or ultra-low-dose RTX protocol ($\leq$500 mg for a cycle, either multiple infusions or a single infusion) to induce the remission and because of lower remission duration and higher relapse rates with this protocol, repeated infusions in three months for treating severe pemphigus patients is recommended.

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All authors contributed to the preparation and finalization of this article.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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