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ORIGINAL PAPER

Comparing early and late treatments with rituximab in pemphigus vulgaris: which one is better?

Kamran Balighi[1] · Maryam Daneshpazhooh[1] · HamidReza Mahmoudi[1] · Mehrnoosh Badakhsh[1] · Amir Teimourpour[1] · Amir Houshang Ehsani[1] · Arghavan Azizpour[1] · Zahra Akbari[1] · Mostafa Mahdavinia[1] · Mojtaba Ghasemiadl[1] · Soheil Tavakolpour[1]

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Abstract

During the last decade, successfully treatment of patients diagnosed with pemphigus vulgaris (PV) with rituximab (RTX) was reported by several authors. The present study has been designed to compare the clinical outcomes and RTX-related side effects between the two groups of early treated (≤6 months) and lately treated PV (>6 months) patients with RTX. We did a retrospective study between Oct 2014 and Jun 2016 to compare the short-term efficacy and safety of RTX in PV diagnosed patients. The primary and secondary endpoints were complete/partial remission of disease and safely tapering of corticosteroids without disease relapse, respectively. Among the 250 RTX exposed PV patients in the selected period, 107 were successfully followed for the mean 19.71 ± 16.78 months. Twenty-four and eighty three have categorized as the early (≤6 months after diagnosis) or lately (>6 months after diagnosis) RTX-treated patients, respectively. A higher rate of complete remission, longer time lasting remission phase, and a lower number of adjuvants were associated with early RTX treatment. Early treatment with RTX might be associated with improvement of clinical effects, but does not seems to be safer than lately RTX therapy. Those in the early treated group may not only have a higher chance to achieve complete remission, but also experience a longer time of disease remission with lower cumulative doses of adjuvant therapy.

Keywords Pemphigus · Rituximab · Anti-desmoglein · Autoimmune bullous disease

Introduction

Pemphigus is a rare autoimmune blistering skin disorders characterized by erosions of the skin and the mucous membrane. Two forms of pemphigus vulgaris (PV) and pemphigus foliaceus (PF) have been well characterized. During the PV, aberrant immune responses target desmogleins (Dsg) 1 and 3, which play an important role in mediating cell-to-cell adhesion [6]. It is a life-threatening condition, which could be fatal if left untreated. Preventing the development of new lesions, healing of old lesions, and reducing the drug-related side effects are the most important objectives of treatment of pemphigus. Finding a treatment with high efficacy and low safety concerns for PV patients was one of the most important goals for the last decades [13, 17]. However, with the emergence of rituximab (RTX), an anti-CD20 monoclonal antibody, successfully treatment of PV patients increased. Nowadays, RTX is recognized as an effective and relatively safe treatment for refractory PV patients [18]. Despite the several conducted studies on the role of RTX in treating PV patients, we are faced with several unanswered questions related to the best approached of RTX therapy. One of these uncertainties, which has been addressed in some limited studies, is related to the best time of starting RTX therapy [3, 9]. Although the results of these studies implying to greater efficacy of RTX when given early in the disease process, more studies are required. During this study, we attempt to suggest some differences between the efficacy and safety of starting RTX within the first 6 months after PV diagnosis or those who have received RTX at least 6 months after PV diagnosis and history of treatment with conventional therapies.

✉ Soheil Tavakolpour
Soheil.tavakolpour@gmail.com

[1] Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran University of Medical Sciences, Vahdate-Eslami Square, Tehran 11996, Iran

Materials and methods

Patients' characteristics

During the Oct 2014–Jun 2016, the records of all the patients with clinical, histological, and immunopathological features of PV, who have experienced treatment with RTX, had been reviewed. All the PV patients have positive direct immunofluorescence (DIF) and also positive anti-Dsg1 ($\geq$ 14 IU/mL) or anti-Dsg3 ($\geq$ 20 IU/mL) in their serum. According to the disease diagnosis and first RTX infusion interval, patients have been categorized as an early treated group (ETG) or late-treated group (LTG). The former group is containing those who exposed to RTX within the first 6 months of disease diagnosis. The latter belongs to those PV patients, who had been exposed to RTX at least 6 months after the diagnosis with PV. The study was designed to be non-interventional, and only patients who agreed to be followed for clinical effectiveness and RTX-related side effects have been included. The study approved by research ethics committees in the Tehran University of Medical Sciences.

Clinical assessment

The main objective was to compare the efficacy and adverse effects of early or late treatment with RTX in PV. In addition to demographic data and critical past medical histories, the response to treatment, safety profiles, anti-Dsg1/3 values, and Pemphigus Disease Area Index (PDAI) was recorded at the baseline, month 3, and the sixth month after the RTX infusion, if the data were available. PDAI is a reliable and accurate disease severity tool to assess pemphigus severity, which was found as a valid scoring system [14]. In addition, during the follow-up, time to reaching remission [complete remission (CR) or partial remission (PR)], possible relapse(s), number of hospitalization(s), and number of adjuvants has been registered. According to the previous consensus [12], patients who had no new or established lesions for at least 2 months were categorized in CR group. However, those who developed transient new lesions, which persist no longer than 1 week had fallen into the PR category. Any patient who achieved either CR or PR was considered as a responder to RTX. The response rate was also defined as the proportion of patients in each group, who responded to RTX, regardless of time to reach remission. In addition, patients who complained of extension of established lesions or have at least three new lesions that do not heal spontaneously within a week were categorized in relapsing group.

Rituximab therapy

All the patients were planned to receive four infusions of RTX at the dose of 500 mg with a 4-week interval. According to the guidelines, all the patients have received premedication prior to RTX to decrease the risk of acute infusion reactions. The primary endpoint was achieving CR/PR as the result of RTX therapy. The secondary endpoints were safely tapering of corticosteroid and discontinuing adjuvant without disease relapse and appurtenance of drug-related side effects.

Statistical analysis

Descriptive analyses were performed by the calculation of means, standard deviation (SD), and proportions. For calculation of adjusted *P* values for other confounder variables, such as follow-up time, logistic regression was used. The analysis of different events over time was performed by Kaplan–Meier curves and log-rank tests. The relationship between variables was tested using Pearson Chi-square, Fisher exact, and 2-samples *T* test or Mann–Whitney, as well as Wilcoxon-signed rank test, depending on the distribution of data (normally or non-normally distribution). All tests were conducted at a significance level of 0.05. Statistical analysis was conducted in SPSS version 21 (SPSS Inc., Chicago, IL, USA).

Results

Patients' demographics and treatment strategies

During the selected period of time, 250 patients were identified with the history of exposure to RTX. However, we could successfully follow 107 of them for a mean of 19.71 ± 16.78 months. Due to different limitations in recording some serological tests and regular clinical examinations, the data related to some patients were incomplete. For example, the PDAI activity score was not recorded for 32 patients at baseline, which has increased to 49 when the third and sixth months considered. Figure 1 demonstrates the number of followed patients for each parameter during the study period and following-up. Twenty-four patients were categorized in the ETG, while 83 patients were related to the LTG. Figure 2 demonstrates the histogram of intervals between the disease diagnosis and RTX infusion. Totally, 52 (48.6%) of included patients were men, and 53 (51.4%) were female, which was comparable. The mean ages in ETG and LTG were 46.52 ± 15.6 and 44.40 ± 12.02 in men and women, respectively. The patients on ETG were followed

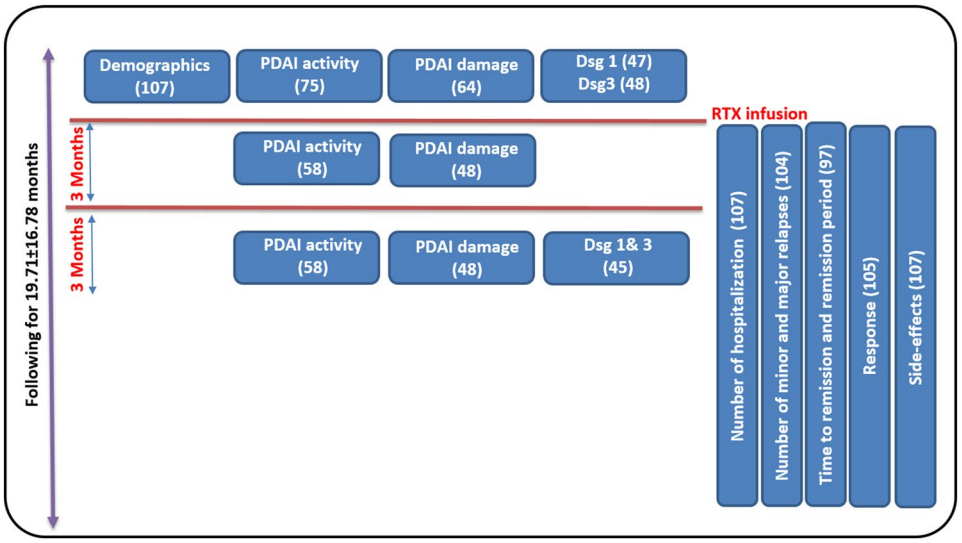

Fig. 1 Number of included/followed patients for each parameter during the study period and following-up

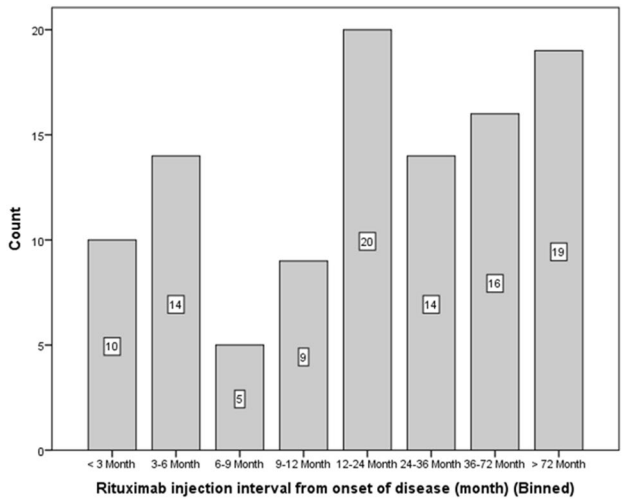

Fig. 2 Distribution of included patients based on interval between the disease diagnosis and RTX infusion

Table 1 Baseline characteristics of all patients

Variables	Early	Late	*P* value
Sex	24	83	
Male (%)	13 (54.14)	41	0.68
Female (%)	11 (45.83)	42	0.68
Disease site (%)			
Mucosal (%)	0 (0)	11 (13.3)	0.072
Cutaneous (%)	7 (29.2)	11 (13.3)	0.079
Mucocutaneous (%)	17 (70.8)	69 (83.1)	0.196
*Age at disease onset ± SD	45.41 ± 15.54	38.00 ± 10.76	**0.03**
Age at treatment ± SD	46.52 ± 15.6	44.40 ± 12.02	0.51
Mean of diagnosis and RTX infusion interval	3.31 ± 1.17	51.7 ± 52.51	< **0.001**
Follow-up (month)	17.35 ± 8.08	19.77 ± 17.77	0.20

Bold values represent statistical significance (< 0.05)

*Age at the disease onset is not necessarily equal to age at the disease diagnosis and initiation of treatment

SD standard deviation

for 17.35 ± 8.08 months, and those in LTG were followed for 19.77 ± 17.77 months, which are not significantly different. Table 1 summarizes the baseline characteristics of all patients.

The treatment strategies were different based on the disease severity and response to treatment. At the time of infusion, prednisolone was started to be tapered in all the patients. Prednisolone tapering schedule was as followed: 25% every 2 weeks; if < 20 mg, 5 mg reduction every 4 weeks, and 1.25 mg reduction every 4 weeks for < 10 mg. However, this protocol was flexible, depending on the response to treatment. If both anti-Dsg1 and anti-Dsg3 became negative, tapering was continued to reach off therapy. Otherwise, prednisolone remained at the dose of 5 mg daily. Regarding adjuvants, the plan was flexible depending on the response to treatment, disease severity, and tolerance of treatment.

Clinical efficacy

Clinical efficacy was evaluated based on four factors, including PDAI scoring at baseline, after 3 and 6 months; response to treatment from either the medical records or during the follow-up. Other followed-up parameters, such as further relapses, remission period, and of anti-Dsg1/3 values at baseline and 6 months after initiation of RTX infusion were also recorded.

Regarding the PDAI, two scores related to disease activity and damage have been recorded at three times for patients.

We have found that PDAI activity scores significantly declined 3 months and 6 months after the RTX infusion in both groups when compared to the baseline values. However, except in LTG after 6 month follow-up (P value = 0.001), no significant difference has been noted among the PDAI damage scores among the groups, evaluated 3 and 6 months following RTX infusion. It is worthy to note that no difference was also found among the baseline and endpoint values (Table 2).

As a result of following patients for at least 9 months, it was observed that early treatment with RTX is not associated with reaching CR (P value = 0.5), PR (P value = 0.06) or totally responding to RTX (P value = 0.8) faster than lately RTX treatment. However, early treatment with RTX was associated with a higher chance of achieving CR, regardless of time to reaching remission (P value = 0.02). In contrast, we found that the number of patients who experienced PR was significantly higher in LTG than the ETG (P value = 0.019). Early treatment with RTX does not significantly increase the chance of responding to treatment (P value = 0.917). Figure 3a, b illustrates the Kaplan–Meier survival curve for time to achieving CR and remission in two groups of ETG and LTG, respectively. Table 3 also shows the response rate to RTX in patients on ETG or LTG.

Furthermore, we evaluated critical followed-up parameters, including the lasting period of remission, minor/major

Table 2 Alteration in clinical and serological parameters following rituximab therapy

	ETG			LTG			Comparison of ETG and LTG
	Baseline	After RTX	P value	Baseline	After RTX	P value	P values after RTX*
PDAI activity (T3)	28.67 ± 19.7	8 ± 9.74	**< 0.001**	25.50 ± 22.82	6.23 ± 7.59	**< 0.001**	0.454
PDAI damage (T3)	3.19 ± 2.34	4.93 ± 3.12	0.077	4.92 ± 2.77	4.76 ± 3.07	0.791	0.868
PDAI activity (T6)	28.67 ± 19.7	3.47 ± 7.41	**< 0.001**	25.50 ± 22.82	2.20 ± 3.29	**< 0.001**	0.382
PDAI damage (T6)	3.19 ± 2.34	3.36 ± 3.23	0.783	4.92 ± 2.77	3.79 ± 2.68	**0.001**	0.662
Total anti-Dsg1 (IU/mL)	82.64 ± 82.59	18.93 ± 54.46	0.086	149.01 ± 143.59	28.41 ± 59.41	**0.003**	0.831
Total anti-Dsg3 (IU/mL)	170.69 ± 57.82	43.54 ± 65.16	**0.011**	174.43 ± 93.39	95.70 ± 82.50	**0.001**	0.054

Bold values represent statistical significance (< 0.05)

ETG early treated group, *LTG* late-treated group, *RTX* rituximab, *T3* after 3 months, *T6* after 6 months

*There was no significant difference in the baseline PDAI in ETG and LTG

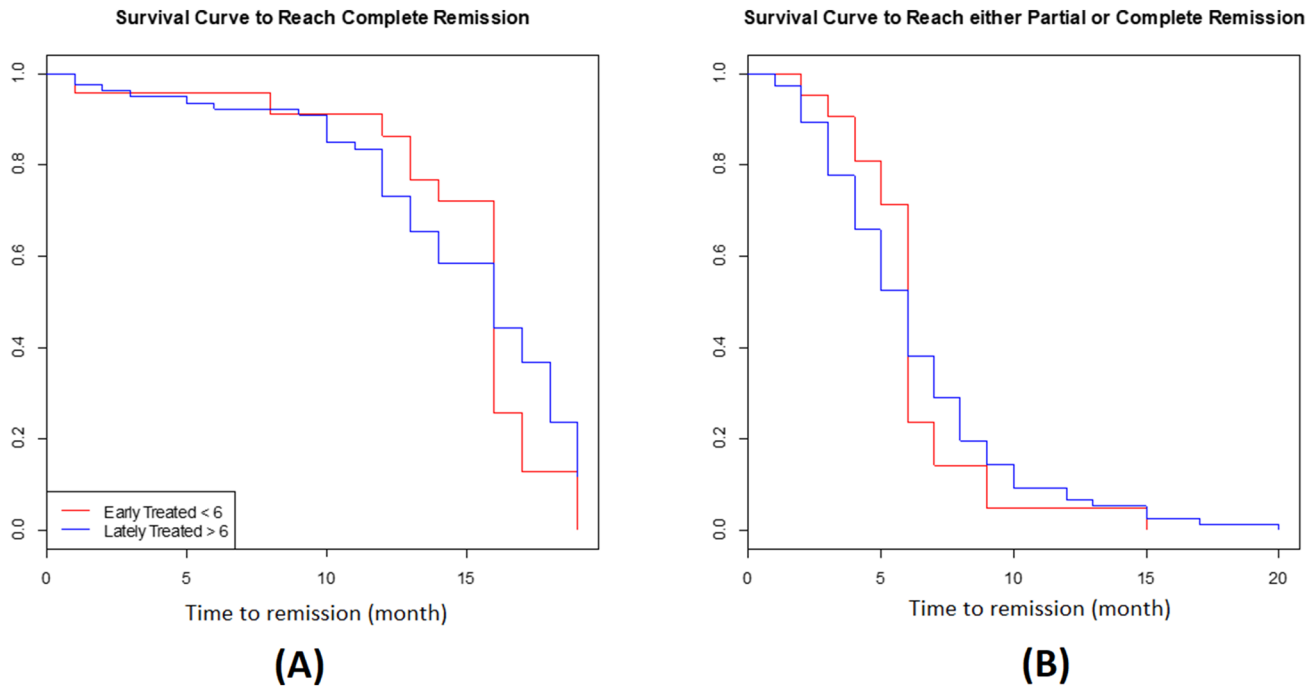

Fig. 3 Kaplan–Meier survival curve for time to reaching **a** complete remission and **b** remission (either complete remission or partial remission) in two group of early–lately treated with rituximab

Table 3 Response rate to rituximab in patients on early or late groups

	Early (23)	Late (82)	*P* value
Response*	22	78	0.917
Complete remission	19	44	**0.020**
Off therapy	3	4	0.179
On therapy	16	40	0.091
Partial remission	3	34	**0.019**
Off therapy	0	2	0.458
On therapy	3	32	**0.029**
No response*	1	4	0.917

Bold values represent statistical significance (< 0.05)

*The response was defined as achieving either complete remission or partial remission regardless of time to reaching remission; and no response was defined as achieving neither complete remission or partial remission

relapses, hospitalizations associated with PV disease after RTX therapy, number of adjuvants regardless of their doses, and finally minimal prednisolone dose during the follow-up period. Mean of remission period was 9.71 ± 3.59 months in ETG and 7.70 ± 8.13 in LTG which was significantly longer in ETG than LTG (*P* value = 0.003). In addition, the number of prescribed adjuvants was significantly lower in ETG than LTG (0.13 ± 0.46 vs. 0.36 ± 0.64; adjusted *P* value = 0.048). However, no difference was found between the minimal doses of prednisolone (ETG: 4.18 ± 2.76 mg/day, LTG 5.46 ± 2.88 mg/day; *P* value = 0.053). After adjusting other time-dependent parameters, no significant difference was found between the occurrence of major relapse (*P* value = 0.855, β = 0.123), minor relapse (*P* value = 0.446, β = 0.531), and treatment with adjuvants (*P* value = 0.079, β = 1.414).

Although the decrease in the anti-Dsg 1/3 values does not mean improvement of PV in all the patients, they could be used as a marker for responding to treatment. In this regard, we found that anti-Dsg1 in the patients in the LTG was significantly more sensitive to RTX therapy than ETG after a 3-month follow-up (*P* value for ETG = 0.086; *P* value for LTG = 0.003). However, Dsg3 seems more sensitive to RTX therapy in both groups (*P* value for ETG = 0.011, *P* value for LTG = 0.001) (Table 2). At the baseline, all the selected patients were comparable, and no difference was detected (*P* value for anti-Dsg1 = 0.533, *P* value for anti-Dsg3 = 1.00). Despite the seroconversion of both Dsg1 and Dsg3 in both groups after a 6-month follow-up, no significant difference was observed among the two groups for each of anti-Dsg1 or anti-Dsg3 values (*P* value for anti-Dsg1 = 0.656, *P* value for anti-Dsg3 = 0.094) (Table 4).

Safety profiles

In addition to efficacy evaluation, we also followed patients for 17.35 ± 8.08 months and 19.77 ± 17.77 months for each of ETG and LTG, respectively. In total, nine patients in ETG (37.5%) and 22 patients (26.5%) experienced some RTX-related side effects. In addition, the type of side effects was also independent of disease diagnosis and RTX administration interval. Infection was reported in four of patients in ETG (16.6%) and nine patients (10.8%) of patients in LTG (*P* value = 0.860). In addition, four of patients in ETG (16.6%) and nine patients (10.8%) of patients in LTG have been suffered from acute infusion reaction (*P* value = 0.860). Adjusting the risk of side effects revealed that early treatment with RTX (≤ 6 months) or late treatment (> 6 months) does not influence the appearance of side effects (*P* value = 0.107). There was a significant between a number of adjuvant with the risk of appearance of side effects (*P* value = 0.001), such that with the addition of one adjuvant, the risk of side-effect occurrence increased 5.2 times. Surprisingly, the disease of three of patients in LTG was flared some weeks/months after the RTX reaction. However, it may be explained by the disease fluctuation and be unrelated to RTX infusion. Table 5 summarizes the safety profile of patients.

Discussion

In this study, we have compared the clinical efficacy and safety profiles of early (≤ 6 months) or late (> 6 months) treatment of PV patients with RTX. Regarding the differences in each group, we have shown that some of the desirable factors related to clinical efficacy, such as higher rate of CR, longer time lasting remission phase, and lower number

Table 4 Frequency of positive and negative anti-Dsg1/3 Ab in patients with who achieved complete remission, partial remission, and non-responder patients

	Anti-Dsg1					Anti-Dsg3				
	Early		Late		*P* value	Early		Late		*P* value
	Positive	Negative	Positive	Negative		Positive	Negative	Positive	Negative	
Baseline	10	8	20	9	0.533	17	1	28	2	1.00
After	1	12	5	27	0.656	5	8	22	10	0.094

Negative Anti-Dsg1: <14 IU/mL; Positive Anti-Dsg1: ≥14 IU/mL; Negative Anti-Dsg3: <20 IU/mL; Positive Anti-Dsg3: ≥20 IU/mL

Table 5 Recorded side effects within 19.71 ± 16.78 months of follow-up

	Early (24)		Late (83)		*P* value
	Yes	No	Yes	No	
Total side effects	9	15	22	61	0.315
Infection	4		9		0.860
Acute injection reaction	4		9		0.860
Exacerbation	0		3		0.277
Other	1		1		0.518

of adjuvants are associated with early treatment with RTX in PV. It may also be explained by the fact that the frequency of more resistant patients to treatment is higher among the LTG. In contrast, a significant reduction of anti-Dsg1 values was associated with the late group, but not an ETG. During the recent years, some of the studies have suggested anti-Dsg1 as a more valuable marker of clinical outcome than anti-Dsg3 in PV patients [1, 4]. However, all these findings need to be confirmed in other studies. We found that after a mean of 8 months following RTX infusion, PV may relapse. In the literature, the mean relapse-time following RTX therapy was reported between 6 and 24 months [5, 8–11]. Our results are somehow consistent with the previous research conducted by Joly et al. [9], which suggested the initiation of RTX maintenance therapy every 6 months rather than 12 months. As it was mentioned, worsening of disease in three cases, which all of them belonged to the LTG was observed. Interestingly, the report of an exacerbation of PV following RTX therapy was reported previously [7, 15]. More studies may make it clear whether it is related to RTX therapy, or not.

Some recently published studies have suggested the use of RTX as the first-line treatment in pemphigus patients [9]. Because of the lack of studies related to first-line line treatment of PV patients with the RTX, even early treatment, employment of RTX in non-refractory cases is still in its infancy. To have a better insight into the priority of RTX therapy in PV patients, we have designed a retrospective study, which consists of 107 patients, who were followed for several months. According to these results, we concluded that RTX is associated with significantly reducing the disease severity, high rate of response, and also decreasing in the levels of anti-Dsg 1/3 titers. Moreover, except disease exacerbation, which does not necessarily related to RTX infusion, no severe side effects more than other immunosuppressive treatment was observed. It is worthy to note that some of the reported side effects in Table 5, except acute infusion reaction, might also be associated with adjuvants. As it was mentioned, the addition of one adjuvant led to the increased risk of side-effect occurrence. This could suggest discontinuing adjuvants after RTX therapy if there is a low risk of disease relapse. It is possible that the better clinical status of those who have received early RTX not be persisted for the subsequent courses of RTX. Although there is no consensus on the risk to benefit ratio of regular therapy with RTX and also optimum intervals, a frequent administration of RTX with an interval of 6–12 months in those who have been treated with early or even first-line RTX might be associated with a long-term remission. In contrast, lack of regular maintenance therapy might decrease the efficacy of RTX therapy in the subsequent courses. Thus, continuing a regular maintenance therapy with RTX might be beneficial for those who have received early RTX therapy and keep the outcomes better than those in the LTG over the long term. This hypothesis is based on the significant decrease in inflammatory responses as well as an increase in regulatory responses following RTX therapy. For example, following B-cell depletion with RTX in patients with lupus nephritis, it was demonstrated that the expression of regulatory responses increased significantly, while the mRNA levels of the involved genes in induction of aberrant responses were profoundly reduced [16]. However, regardless of transitory changes in the immune response in favor of disease remission, returning them to baseline levels is the main concern. In this regard, Ahmed et al. [2] have shown that regular treatment with a combination of RTX and IVIg in PV patients for several infusions could lead to a prolonged, sustained remission without additional systemic therapy. This positive clinical outcome was suggested to be the result of pathogenic B-cell depletion and then restoration of immune regulation [2]. Further studies with regular treatment with RTX monotherapy in PV may shed light on its long-term efficacy.

Considering the fact that this study was designed to be observational, but not interventional, we have faced some limitations. Because of receiving prednisolone, adjuvants, and RTX in some patients at the same time, some of the reported clinical outcomes and side effects may not be purely related with RTX. In addition, despite following-up all the patients for response to treatment by regular clinical examinations and probable side effects either by clinical examination or by calling to the patient, we were not able to record Dsg 1/3 levels as well as PDAI scores for all the included patients. This could negatively influence the results. A combination of a retrospective study and prospectively following-up of patients may be one of the reasons for the lack of some records. Different periods of follow-up for each patient could also influence the results when compared to the study that follows all the patients for a fixed period of time. Future studies with a fixed and longer follow-up, inclusion of all the serological and clinical marker, as well as categorizing groups not only based on disease diagnosis and RTX therapy intervals but also considering the steroid doses

and adjuvants are encouraged. These could significantly help for shedding light into advantages and disadvantages of both early and late RTX administrations.

In conclusion, we have shown that patients under early treatment with RTX (≤6 months) may not only have a higher chance to achieve CR but also experience a longer time of disease remission. However, further studies containing a higher number of patients and also a long follow-up period are required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study approved by research ethics committees in the Tehran University of Medical Sciences.

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