Real world evidence: Patients with refractory pemphigus treated with Rituximab

Vagiani Perifani a,1, Maria Dalamaga a,b,*,1, Konstantinos Theodoropoulos a, Sofia Theotokoglou a, Anna Syrmali a, Panagiota Loumou a, Evangelia Papadavid a, **

a 2nd Department of Dermatology and Venereology, Unit of Autoimmune Skin Disorders, Attikon General University Hospital, Medical School, National and Kapodistrian University of Athens, Rimini 1, Chaidari 124 62, Athens, Greece
b Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Mikras Asias 75, 115 27, Athens, Greece

ARTICLE INFO

Keywords:
Autoimmune blistering disease
Biologic
Efficacy
Immunosuppression
Pemphigus
Rituximab
Safety

ABSTRACT

Background: Pemphigus is a group of autoimmune blistering diseases, potentially life-threatening. Rituximab received FDA approval in June 2018 for the treatment of moderate to severe pemphigus vulgaris.

Objectives: To evaluate the efficacy and safety of rituximab in patients with pemphigus, resistant to previous therapies or unable to receive classic immunosuppressive treatment due to serious adverse events or comorbidities.

Materials and methods: Twenty-five patients (9 men, 16 women), mean age 49.4 ± 15.9 years (range 21–74 years), mean disease duration 4 ± 2.7 years (range 0.25–10 years) were included in the study: 19 patients with pemphigus vulgaris and 6 with pemphigus foliaceous. The efficacy of rituximab was evaluated according to the control of disease, retention of remission, disease severity, previous treatments and adverse reactions. During COVID-19 pandemic patients are monitored closely through tele-dermatology.

Results: Twenty-three out of 25 patients had great improvement, 2 out of 25 ceased therapy due to adverse events (arthralgias and dyspnea). Sixteen out of 23 received additional course after 8 months (range 5–60 months).

More aged patients presented more frequently adverse events and underwent additional courses (p = 0.002). Rituximab was found superior to classic immunosuppressive treatment in terms of efficacy and safety, with larger periods of remission and lower doses of corticosteroids and immunosuppressants. No major adverse events were noticed.

Conclusions: Rituximab is a very effective treatment of pemphigus and, remarkably, superior to classic immunosuppressive treatment.

1. Introduction

Pemphigus constitutes a group of rare autoimmune blistering diseases, characterized histopathologically by intraepithelial blisters and acantholysis, and immunologically by circulating autoantibodies against the surface of epidermal cells. The main lesions are flaccid blisters and erosions of the mucous membrane and the skin [1–3]. Pathophysiologically, the intraepithelial blisters are formed by IgG autoantibodies against two adhesion proteins, desmoglein 3 and/or desmoglein 1 on epidermal keratinocytes [4,5]. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the two main types of the pemphigus group, with the former affecting the skin and mucous membranes, and the latter affecting only the skin. Pemphigus vulgaris is characterized by autoantibodies against desmoglein 3 and/or desmoglein 1 while pemphigus foliaceus is characterized almost exclusively by autoantibodies against desmoglein 1 [5].

The objectives of the therapeutic management of pemphigus include: 1) the control of the activity of the disease; 2) the healing of the lesions of skin and mucous membranes; and 3) the minimization of the relapses and the adverse effects of the treatment [6]. Although the treatment
with systemic corticosteroids presents many adverse effects, it has remained the first-line treatment for pemphigus for many years [7–9]. Moreover, therapeutic adjuvants, just as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, cyclophosphamide and high-dose intravenous immunoglobulins (IVIG), can be used for their steroid-sparing effects [1–3].

During the past years, more interest has been shown in shifting from conventional to more targeted therapies for the treatment of autoimmune diseases. Biologic drugs, including monoclonal antibodies such as rituximab, have been used as targeted drug therapy in managing various autoimmune diseases [7–9]. Rituximab is a chimeric monoclonal antibody that targets CD20 surface antigen of B-lymphocytes resulting in their destruction and the inhibition of their evolution to plasmacytoses from which the antibodies are produced from. It was first approved for the treatment of non-Hodgkin’s lymphoma in adults and then for rheumatoid arthritis (RA), Wegener granulomatosis and microscopic polyangiitis [7–9]. Moreover, rituximab has gained FDA approval from June 2018 for the treatment of adults with moderate to severe PV, while, in Europe, it was administrated only in experienced centers after written approval from the respective National Drug Organization (in Greece EOF).

The Autoimmune Skin Disease Unit of the 2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens has been treating patients with pemphigus since 2005, and the use of rituximab was initiated in 2008, with a four-course protocol and a maintenance course 6 months later in steroid resistant pemphigus patients [10]. The purpose of the present study is to evaluate the efficacy and safety of rituximab in patients with pemphigus, resistant to previous therapies or unable to receive classic immunosuppressive treatment due to serious adverse events or comorbidities.

2. Materials and Methods

2.1. Selection of patients

A total of 25 patients with PV and PF admitted, hospitalized and treated with rituximab in our Department from 2008 until September 2018 were enrolled in this study, regardless age, sex and race. The inclusion criteria were proven cases of PV and PF in persons over 18 years of age. This study does not include outcomes from 2018 till now; however, we followed up patients for adverse events but no such events were recorded.

The clinical and demographic features of patients were recorded. Moreover, the duration of the disease, previous treatments and their side effects were recorded from the medical records of the patients. The extend of skin/mucosal involvement was clinically assessed with Pemphigus Disease Area Index (PDAI) score for each patient. Patients were examined in order to assess the severity of the disease according to the PDAI tool, which is internationally accepted as an index for disease activity [11]. The diagnosis was confirmed clinically and histopathologically with skin biopsy from the lesions.

There are two different protocols, one lymphoma and another for RA [8,9]. Rituximab (MabThera-Roche) was given according to the lymphoma protocol, where a total dose of 375 mg/m² was administered in four weekly intravenous infusions, as it was already administered in our hospital based on the experience from the Hematologic Department. All patients received therapy with acyclovir (400 mg twice a day) and trimethoprim/sulfamethoxazole (400 mg/80 mg once a day) during the treatment with rituximab and two months after the end of the treatment as a prophylactic treatment against bacterial infections, herpes simplex virus infection and varicella zoster virus infection. Patients who were already treated with systemic corticosteroids and immunosuppressants were tapered later in a period of two to three months, according to the daily dosage of corticosteroids and the duration of their therapeutic use.

The patients selected for the treatment with rituximab met the following criteria: 1) lack of response and dependence on systemic corticosteroids and immunosuppressive treatment; 2) serious side effects caused by the long treatment with systemic corticosteroids and immunosuppressive agents. All patients had written approval from the National Drug Organization for the administration of rituximab. Pregnant women or women during the breastfeeding period were excluded from the study. Previous treatment with rituximab for other reasons, history of malignancy, active and serious infections, such as active Hepatitis B, active Hepatitis C and Interferon-Gamma Release Assay (IGRA) positivity were also exclusive criteria. All patients gave written informed consent. This clinical study was approved by the Scientific and Ethical Committee of the hospital.

2.2. Statistical analysis

Descriptive characteristics of pemphigus cases are presented as proportions for categorical and ordinal variables and as mean ± standard deviation (SD) or median and range for continuous variables. Comparisons between cases and controls were conducted by using chi-square tests for categorical variables and t-test or Mann–Whitney test for normally or not normally distributed continuous variables respectively. Statistical analysis of the data was performed with IBM-SPSS® version 24 for Windows.

3. Results

Table 1 depicts baseline features of 25 patients with pemphigus: 9 were males and 16 females with a mean age of 49.4 ± 15.9 years (range 21–74 years). Nineteen patients suffered from PV and 6 from PF with a mean disease duration before rituximab administration of 4 ± 2.7 years (range 0.25–10 years). Median baseline PDAI score was 41 (range 16–122) revealing moderate to severe pemphigus [11]. We also evaluated patients at 3 months and their median PDAI score was 13 (range 7–28). Fig. 1A, B, 2A and 2B show clinical presentations of two patients with PV before and after 3-month treatment with rituximab. Fig. 3A and B depict clinical presentations of one patient with PF before and after 3-month treatment with rituximab. All patients had received systemic corticosteroids (each patient with different prednisone/day dose based

| Table 1 | Baseline features of 25 patients with pemphigus. |
|-----------------|-----------------|
| **Mean age ± SD (years)** | 49.4 ± 15.9 |
| **Gender (n, %)** | |
| Male | 9 (36) |
| Female | 16 (64) |
| **Diagnosis (n, %)** | |
| Pemphigus vulgaris | 19 (76) |
| Pemphigus foliaceus | 6 (24) |
| **Mean duration of disease ± SD (years)** | 4 ± 2.7 |
| **Baseline PDAI score (median, range)** | 41 (16–122) |
| **PDAI score at 3 months (median, range)** | 13 (7–28) |
| **PDAI score at relapses (median, range)** | 25 (17–34) |
| **Previous treatments (n, %)** | |
| Systemic corticosteroids | 25 (100) |
| Azathioprine | 22 (88) |
| MMF (mycophenolate mofetil) | 12 (48) |
| IVIG | 5 (20) |
| Cyclosporine | 4 (16) |
| Plasmapheresis | 5 (20) |
| Methotrexate | 2 (8) |
| Cyclophosphamide | 2 (8) |
| Infliximab | 1 (4) |
| **Outcome of first session (n, %)** | |
| Improvement | 23 (92) |
| Cease due to adverse events | 2 (8) |
| **Time from first session to additional course, median (range) (months)** | 8 (5–60) |
| **Additional course (n, %)** | |
| Systemic corticosteroids | 16 (64) |
| **Number of additional courses (median, range)** | 1 (1–6) |
| **Reason of additional course (n, %)** | |
| Relapse | 11 (44) |
| Prevention | 5 (20) |
Fig. 1. A & 1B: Clinical presentations of one patient with PV before and after 3-month treatment with rituximab.

Fig. 2. A & 2B: Clinical presentations of one patient with PV before and after 3-month treatment with rituximab.

Fig. 3. A & 3B: Clinical presentations of one patient with PF before and after 3-month treatment with rituximab.
on his/her weight) and one or more immunosuppressants, such as azathioprine, mycophenolate mofetil, IVIG and plasmapheresis, without control of the disease, leading to multiple side effects due to the prolonged steroid intake.

Table 2 shows the frequency of the recorded side effects from previous treatments. The two most common adverse effects were osteoporosis/osteopenia and Cushing syndrome, followed by diabetes mellitus and ophthalmologic disorders. We haven’t recorded any side effect of any kind (infections including recurrence or relapses from HSV and herpes zoster, etc) at the onset and during the follow up period in patients that completed the treatment with rituximab.

From the total of 25 patients, 23 of them completed the therapy and 2 of them ceased it due to adverse events (one patient presented arthralgias after the second infusion and the other presented dyspnea during the first infusion). All 23 patients had great improvement after the treatment but 16 of them received additional course of 375 mg/m² to relapse (11 patients, 44%) or prevention of relapse (5 patients, 20%), after 8 months (range 5–60 months). Median PDAI score at relapses was 25 (range 17–34).

Generally, there was no association of clinical characteristics and age category (more than 50 years and less than 50 years). However, more aged patients tended to present more frequently osteoporosis (p = 0.04), diabetes mellitus (p = 0.005) and infections (p = 0.011) as side effects of previous treatments, and underwent additional course of treatment (p = 0.002). Additionally, there was no association of clinical characteristics and gender. Nevertheless, males presented more often ophthalmologic disorders (p = 0.048) and higher PDAI scores than females (p = 0.06, borderline statistical significance). Also, pemphigus type was not associated with clinical characteristics and side effects. However, PV patients presented a more frequent association with diabetes mellitus (p = 0.049) than patients with PF.

Finally, Table 3 presents all the baseline features of our patients, such as age, gender, duration of pemphigus, PDAI scores, previous treatments and their side effects. Table 4 depicts the treatment features of each patient such as the outcome after the first session, sides effects, the need of additional course or not and the time period between the end of the first session and the additional course.

4. Discussion

In the present study, we have shown that rituximab is a safe and highly effective therapeutic approach in refractory pemphigus with achievement of complete response in almost all patients after the completion of four courses of 375 mg/m² of rituximab. Maintenance treatment has been used in the beginning for the relapse prevention (5 out of 25 patients) and later only in some patients (11 out of 25) due to disease relapse [10]. Rituximab was well tolerated; only two patients withdrew due to adverse events which were not relevant to rituximab. One patient had arthralgia during the second course and the other patient presented dyspnea (caused by pulmonary edema) during the first course. Interestingly, more aged patients tended to present more frequently with osteoporosis, diabetes mellitus and infections as side effects and underwent additional course of treatment. Adverse events from previous treatments were more severe, the two most common were osteoporosis/osteopenia and Cushing syndrome, followed by diabetes mellitus and ophthalmologic disorders. No other major or life-threatening adverse events were observed during or after the treatment with rituximab, which is in agreement with the literature [12-17]. Moreover, there were no infections or sepsis in our patients during or after the completion of the treatment.

In our previous study [10], we have investigated the use of rituximab as a maintenance therapy for relapse prevention with an additional course of 375 mg/m² administered intravenously in our clinic 6 months after the end of the four-course treatment (without the reintroduction of other systemic medication). We have shown no benefit of using rituximab for relapse prevention, and since then we have administered rituximab only at disease relapse. In our cohort, 5 patients received rituximab for relapse prevention and 11 patients received at least one additional course due to disease relapse, which is in agreement with the results from single centers showing that most patients received at least one additional course [12-14].

Most patients had severe pemphigus; 16 of them had PDAI score between 15 and 45 showing significant pemphigus form, and 9 of them had PDAI score between 45 and 263 revealing extensive pemphigus form [11]. Moreover, more aged patients presented more frequently comorbidities, such as osteoporosis, diabetes mellitus and infections. All these were side effects due to the previous use of systemic treatments. Agarwal et al. showed that rituximab not only decreased prednisolone intake dramatically but it also provided a shorter time to complete remission when compared to classic immunosuppressive treatments [17]. Therefore, rituximab presents an advantage for aged patients, for patients who do not respond to high dose steroids and for patients with other comorbidities.

Rituximab provides clinical improvement with fast initial response, longer disease-free periods compared to classic immunosuppressive therapy. The first report of rituximab therapy in a patient with PV was published in 2002 [18]. Since then, various case reports, case series and studies have shown quite promising results in pemphigus patients who did not respond to standard therapy [19-24], and many patients were treated successfully with rituximab. All these trials have concluded that: 1) rituximab therapy shows an obvious clinical improvement; 2) decreased doses of corticosteroids are needed, and 3) prolonged periods of clinical remission are reported.

Zakka et al. reviewed 42 studies published between 2000 and 2012 on rituximab therapy in a total of 272 patients with refractory pemphigus [25], and found 180 patients treated according to the lymphoma protocol and 92 patients according to the RA protocol. This review showed that patients treated with the lymphoma protocol had lower rates of response, relapse and serious infections [25]. On the other hand, patients treated with the RA protocol had higher rate of response, relapse and infections. Another review by Amber and Hertl showed no significant difference in patients achieving complete remission between patients treated with the lymphoma protocol and those treated with the RA protocol [26]. Moreover, rituximab treatment according to the lymphoma protocol was superior based on the risk for relapse. On the contrary, a meta-analysis from Wang et al. found that high-dose rituximab treatment was associated with a longer duration of complete remission than low-dose rituximab treatment [27]. There was no superiority of the lymphoma over the RA treatment protocol or of high-dose over low-dose rituximab for any other outcome [27].

There are some limitations of our study including its retrospective nature, the small number of patients, the lack of quality of life (QoL) measures, the lack of a control group and the single center trial. Pemphigus diagnosis was based on immunologic (direct and indirect immunofluorescence) and clinical characteristics, as we did not have the possibility of measuring pemphigus autoantibodies against desmoglein

| Side Effects                        | N (%) |
|------------------------------------|-------|
| Osteoporosis/Osteopenia            | 11 (44) |
| Spontaneous fractures              | 2 (8) |
| Anxiety and Depression disorders   | 5 (20) |
| Hypertransaminemia                 | 3 (12) |
| Cushing syndrome                   | 11 (44) |
| Diabetes mellitus                  | 8 (32) |
| Ophthalmological disorders         | 8 (32) |
| Menstrual disorders                | 2 (12.5) in 16 females |
| Infections                         | 7 (26) |
| Hypertension                       | 4 (16) |
| Secondary adrenal insufficiency     | 2 (8) |
Table 3
Baseline features of 25 patients with pemphigus.

| Patient number | Sex | Age (years) | Diagnosis | Duration of disease (years) | Initial PDAI score (0–263) | Previous Treatments | Side events from previous treatments |
|----------------|-----|-------------|-----------|-----------------------------|-----------------------------|---------------------|--------------------------------------|
| 1              | M   | 55          | PV        | 2.5                         | 122                         | CS, AZA, MMF, IVIg, plasmapheresis, infliximab | Osteoporosis, Cushing syndrome, DM, anxiety and depression disorders, ophthalmological disorders, infections, hypertension, ophthalmological disorders, infections |
| 2              | M   | 66          | PV        | 1                           | 33                          | CS, AZA, MMF, plasmapheresis, MTX, cyclophosphamide | Osteoporosis, anxiety and depression disorders, DM, ophthalmological disorders, infections |
| 3              | F   | 74          | PV        | 0.5                         | 34                          | CS, AZA, MMF | Osteoporosis, DM |
| 4              | F   | 64          | PV        | 1                           | 42                          | CS, AZA, MMF, cyclosporine | DM, hypertransaminemia, infections |
| 5              | F   | 59          | PV        | 8                           | 16                          | CS, MMF | Osteoporosis, spontaneous fractures, DM |
| 6              | F   | 51          | PV        | 6                           | 32                          | CS, AZA, MMF, cyclosporine, plasmapheresis | Cushing syndrome |
| 7              | M   | 53          | PV        | 7                           | 105                         | CS, AZA, cyclophosphamide, plasmapheresis | Cushing syndrome, DM, ophthalmological disorders, infections |
| 8              | F   | 46          | PF        | 2                           | 35                          | CS, AZA, MMF | Hypertransaminemia, ophthalmological disorders, hypertension |
| 9              | F   | 32          | PV        | 5                           | 18                          | CS, AZA, MMF, IVIg, plasmapheresis, cyclophosphamide | Osteoporosis, spontaneous fractures, anxiety and depression disorders, Cushing syndrome, ophthalmological disorders, menstrual disorders |
| 10             | M   | 72          | PV        | 6                           | 35                          | CS, AZA | Cushing syndrome, DM, hypertension |
| 11             | M   | 57          | PV        | 10                          | 34                          | CS, AZA | Osteoporosis, Cushing syndrome, ophthalmological disorders, infections |
| 12             | F   | 24          | PV        | 4                           | 46                          | CS, AZA, MMF | Anxiety and depression disorders, Cushing syndrome, ophthalmological disorders, menstrual disorders, hypertension, secondary adrenal insufficiency |
| 13             | F   | 55          | PV        | 6                           | 44                          | CS, AZA | Osteoporosis, Cushing syndrome, infections, secondary adrenal insufficiency |
| 14             | M   | 37          | PV        | 1                           | 90                          | CS, MMF | Anxiety and depression disorders, ophthalmological disorders |
| 15             | M   | 65          | PV        | 2                           | 50                          | CS, AZA | DM |
| 16             | F   | 21          | PV        | 6                           | 43                          | CS, AZA, plasmapheresis | Osteoporosis |
| 17             | F   | 35          | PF        | 2                           | 28                          | CS, AZA | None recorded |
| 18             | M   | 36          | PF        | 5                           | 34                          | CS, AZA | None recorded |
| 19             | F   | 67          | PV        | 7                           | 36                          | CS, AZA, MMF | Osteoporosis, Cushing syndrome, secondary adrenal insufficiency |
| 20             | F   | 23          | PV        | 0.25                        | 99                          | CS, AZA, IVIg | None recorded |
| 21             | F   | 57          | PF        | 6                           | 49                          | CS, AZA | Osteoporosis, Cushing syndrome, infections |
| 22             | M   | 52          | PF        | 2                           | 66                          | CS, AZA, IVIg, cyclosporine | None recorded |
| 23             | M   | 52          | PV        | 0.66                        | 41                          | CS, AZA, MMF, IVIg | Osteoporosis |
| 24             | F   | 45          | PF        | 4                           | 22                          | CS, AZA | None recorded |
| 25             | F   | 27          | PV        | 5                           | 47                          | CS, AZA, MMF, MTX | Cushing syndrome, hypertransaminemia |

Abbreviations: AZA: azathioprine; CS: systemic corticosteroids; DM: diabetes mellitus; F: female; M: male; MMF: mycophenolate mofetil; MTX: methotrexate; PF: pemphigus foliaceous; PV: pemphigus vulgaris.

Table 4
Treatment features of patients with pemphigus (N = 25).

| Patients number | Outcome after first session | Side events after first session | Additional courses | Number of additional courses | Time from first session to additional course (months) | Reason of additional courses |
|-----------------|----------------------------|--------------------------------|-------------------|----------------------------|-----------------------------------------------------|-----------------------------|
| 1               | Improvement                 | None                           | Yes               | 5                          | 6                                                   | Relapse                     |
| 2               | Improvement                 | None                           | Yes               | 6                          | 9                                                   | Prevention                  |
| 3               | Improvement                 | None                           | Yes               | 1                          | 6                                                   | Prevention                  |
| 4               | Improvement                 | None                           | Yes               | 2                          | 9                                                   | Relapse                     |
| 5               | Improvement                 | None                           | Yes               | 4                          | 6                                                   | Relapse                     |
| 6               | Improvement                 | None                           | Yes               | 1                          | 9                                                   | Prevention                  |
| 7               | Improvement                 | None                           | Yes               | 1                          | 6                                                   | Relapse                     |
| 8               | Improvement                 | None                           | Yes               | 4                          | 8                                                   | Relapse                     |
| 9               | Stopped treatment           | Arthralgia                     | –                 | –                          | –                                                   | –                           |
| 10              | Stop treatment              | Pulmonary edema                | –                 | –                          | –                                                   | –                           |
| 11              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
| 12              | Improvement                 | None                           | Yes               | 1                          | 8                                                   | Prevention                  |
| 13              | Improvement                 | None                           | Yes               | 1                          | 10                                                  | Prevention                  |
| 14              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
| 15              | Improvement                 | None                           | Yes               | 1                          | 60                                                  | Relapse                     |
| 16              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
| 17              | Improvement                 | None                           | Yes               | 1                          | 8                                                   | Relapse                     |
| 18              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
| 19              | Improvement                 | None                           | Yes               | 3                          | 8                                                   | Relapse                     |
| 20              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
| 21              | Improvement                 | None                           | Yes               | 1                          | 8                                                   | Relapse                     |
| 22              | Improvement                 | None                           | Yes               | 2                          | 5                                                   | Relapse                     |
| 23              | Improvement                 | None                           | Yes               | 1                          | 8                                                   | Relapse                     |
| 24              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
| 25              | Improvement                 | None                           | No                | –                          | –                                                   | –                           |
In conclusion, our experience from the Autoimmune Skin Diseases Unit shows that rituximab is a safe choice being highly effective as a treatment for refractory pemphigus. Patients treated with rituximab have clinical improvement with fast initial response and longer disease-free periods compared to classic immunosuppressive therapy. Smaller amounts of systemic corticosteroids are needed and fewer side effects from the treatment are recorded.

Funding

No funding was received for this study.

Declaration of competing interest

None.

References

[1] Joly P, Litrowski N. Pemphigus group (vulgaris, vegetans, foliaceus, herpetiformis, brasiliensis). Clin Dermatol 2011;29:432–6.
[2] Kleesel A, Hertl M. Autoimmune bullous skin diseases. Part 1: clinical manifestations. J Dtsch Dermatol Ges 2011;9:844–56. quiz 857.
[3] Kleesel A, Hertl M. Autoimmune bullous skin diseases. Part 2: diagnosis and therapy. J Dtsch Dermatol Ges 2011;9:927–47.
[4] Hertl M, Jedlickova H, Karpati S, Marinovic R, Uzun S, Yayli S, Mimmoun D, Borradori L, Feliciani C, Ioannides D, Joly P, Kowalewski C, Zambruno G, Zillikens D, Jonkman MF, Pemphigus. S2 guideline for diagnosis and treatment—guided by the European dermatology forum (EDF) in cooperation with the European academy of dermatology and Venerology (EADV). J Eur Acad Dermatol Venereol 2015;29:605–14.
[5] Amagai M, Klaus-Kovtun V, Stanley JR. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. Cell 1991;67:869–79.
[6] Tavakolpour S, Mamouani H, Balighi K, Bedini R, Daneshzapooh M. Sixteen-year history of rituximab therapy for 1085 pemphigus vulgaris patients: a systematic review. Int Immunopharm 2018;54:131–8.
[7] Tavakolpour S. Anti-interleukin and associated receptors monoclonal antibodies therapy in autoimmune diseases. Receptors Clin Investig 2016;3:1173.
[8] Grillo-Lopez AJ, White CA, Varns C, Shen D, Wei A, McClure A, Dallaire BK. ´Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma. Semin Oncol 1999;26(Suppl 14): 66–72.
[9] Teng YK, Huizinga TW, van Laar JM. Targeted therapies in rheumatoid arthritis: focus on rituximab. Biologics 2007;1:325–33.
[10] Gregorio S, Giartrazou S, Theodoropoulos K, Katsolis A, Loumou P, Toubmis-Ioannou E, Papadavid E, Averinou G, Stavrianas N, Rigopoulos D. Pilot study of 19 patients with severe pemphigus: prophylactic treatment with rituximab does not appear to be beneficial. Dermatology 2014;228:158–65.
[11] Boulard C, Duverte Lehembr S, Picard-Dahan C, Kern JS, Zambruno G, Feliciani C, Marinovic B, Vabres P, Borradori L, Prot-Souchon C, Labellille B, Richard MA, Ingen-Housz-Oro S, Huizet E, Werth VP, Murrell DF, Hertl M, Benichou J, Joly P, International Pemphigus Study Group. Calculation of cut-off values based on the Autoimmune Bullous Skin Disorder Intensity Score (ABSSID) and Pemphigus Disease Area Index (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. Br J Dermatol 2016;175:142–9.
[12] GI Cianchini, Lupi F, Masini C, Corona R, Puddu P, De Pita O. Therapy with rituximab for autoimmune pemphigus: results from a single-centre observational study on 42 cases with long-term follow-up. J Am Acad Dermatol 2012;67:617–22.
[13] Kazperkiewicz M, Shinarovitch I, Ludwig RJ, Rose C, Zillikens D, Schmidt E. Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. J Am Acad Dermatol 2011;65:552–8.
[14] Kim TH, Choi Y, Lee SE, Lim JM, Kim SC. Adjuvant rituximab treatment for pemphigus: a retrospective study of 45 patients at a single center with long-term follow up. J Dermatol 2017;44:615–20.
[15] Cianchini G, Corona R, Frezzolini A, Ruffelli M, Didona B, Puddu P. Treatment of severe pemphigus with rituximab: report of 12 cases and a review of the literature. Arch Dermatol 2007;143:1033–8.
[16] Uzun S, Bilgic Temel A, Akman Karaaksa A, Ergin E, Ozkesici B, Eskicioglu AH, Ertan A, Ugurlu N, Nazlim B, Kos C, Bozkurt S, Dicle O, Aliyev E, Yilmaz E. Efficacy and safety of rituximab therapy in patients with pemphigus vulgaris: first report from Turkey. Int J Dermatol 2016;55:1362–8.
[17] Agarwal A, Hall 3rd RP, Banet IL, Cardones AR. Comparison of rituximab and conventional adjuvant therapy for pemphigus vulgaris: a retrospective analysis. PLoS One 2018;13:e0198074.
[18] Salopek TG, Lopetty S, Tredget EE. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. J Am Acad Dermatol 2002;47:785–8.
[19] Balighi K, Daneshzapooh M, Kherzi S, Mahdavi-nia M, Hajisedery-javadi M, Chams-Davatchi V. Adjuvant rituximab in the treatment of pemphigus vulgaris: a phase II clinical trial. Int J Dermatol 2013;52:862–7.
[20] Cho HH, Jin SP, Chung JH. Clinical experiences of different dosing schedules of rituximab in pemphigus with various disease severities. J Eur Acad Dermatol Venereol 2013;28:186–91.
[21] Kazperkiewicz M, Eming R, Behzad M, Hunzelmann N, Meurer M, Schulte-Korges H, von Wrousow P, Hertl M, Zillikens D, Freivogel K, Dorner T, Schmidt E. Efficacy and safety of rituximab in pemphigus: experience of the German Registry of Autoimmune Diseases. J Dtsch Dermatol Ges 2012;10:727–32.
[22] Kim JH, Kim YH, Kim MR, Kim SC. Clinical efficacy of different doses of rituximab in the treatment of pemphigus: a retrospective study of 27 patients. Br J Dermatol 2011;165:646–51.
[23] Lunardon L, Tsai KJ, Propert KJ, Fett N, Stanley JR, Werth VP, Tsai DE, Payne AS. Adjuvant rituximab therapy of pemphigus: a single-center experience with 31 patients. Arch Dermatol 2012;148:1031–6.
[24] Reguial Z, Tabary T, Maizieres M, Bernard P. Rituximab treatment of severe pemphigus: long-term results including immunologic follow-up. J Am Acad Dermatol 2012;67:623–9.
[25] Zakka LR, Shetty SS, Ahmed AR. Rituximab in the therapy of pemphigus vulgaris. Dermatol Ther 2012;2:1–13.
[26] Amber KT, Hertl M. An assessment of therapy history and its association with clinical outcomes and relapse in 155 pemphigus patients with response to a single cycle of rituximab. J Eur Acad Dermatol Venereol 2015;29:777–82.
[27] Wang HH, Liu CW, Li YC, Huang YC. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. Acta Derm Venereol 2015;95:926–32.
[28] Shakshouk H, Daneshzapooh M, Murrell DF, Lehmans JS. Treatment considerations for patients with pemphigus during the COVID-19 pandemic. J Am Acad Dermatol 2020;82:e235–6.
[29] Kazperkiewicz M, Schmidt E, FAIRLEY JA, Joly P, Payne AS, Vele ML, Zillikens D, Woodley DT. Expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic. J Eur Acad Dermatol Venereol 2020;34:e302–3.