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REVIEW

Rituximab in the Treatment of Pemphigus Vulgaris

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ABSTRACT

Introduction: Rituximab is increasingly used in patients with pemphigus vulgaris (PV) who are nonresponders to conventional therapy.

Methods: A PubMed search was conducted using the words pemphigus vulgaris and rituximab therapy from papers published between 2000 and 2012. Two protocols were used. In the lymphoma protocol, patients received four weekly infusions of rituximab (dose 375 mg/m^2). The rheumatoid arthritis (RA) protocol consisted of two infusions of 1,000 mg each 15 days apart. The variables recorded from each study included clinical remission off or on therapy, relapse rate, incidence of serious adverse events, concomitant therapies, duration of follow-up, and when available, levels of B cells and autoantibodies.

Results: Forty-two studies were found, which reported 272 patients; 180 were treated by the lymphoma protocol and 92 by the RA protocol. Both protocols were effective in treating recalcitrant PV. The lymphoma protocol had a lower response rate, relapse rate and serious infections, but higher mortality, and there were nonresponders. The RA protocol produced a higher response rate, relapse rate, number of infections, but lower mortality rate, and lacked nonresponders. The cumulative follow-up for patients treated with the lymphoma protocol was 15.44 months (range 1–41) and 21.04 months (range 8.35–29) for the RA protocol. A major concern in both protocols was the high infection rates, some of which were fatal. A different protocol using a combination of rituximab with intravenous immunoglobulin in a defined manner with a definitive endpoint, used in a limited cohort of patients, showed promising results.

Conclusion: Neither protocol produced a sustained clinical remission and both required continued systemic therapy. Before initiation of treatment, physicians should have a specific

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goal and endpoint and be aware of its potential side effects and lack of information on its long-term effects. Patients should be carefully monitored during and after therapy.

Keywords: Clinical outcomes; Immunology and inflammatory skin diseases; Lymphoma protocol; Pemphigus vulgaris; Rheumatoid arthritis protocol; Rituximab

INTRODUCTION

Pemphigus vulgaris (PV) is a potentially fatal autoimmune mucocutaneous blistering disease that involves the skin and the mucous membranes [1]. PV is a rare disease with an incidence of approximately 0.1–3.2 cases per 100,000 individuals annually worldwide [2]. It is a disease of the middle-aged population, typically occurring after the age of 50 years, although some cases have been reported in younger adults and children [3]. PV is seen more frequently in people of Mediterranean decent and Ashkenazi Jews [4]. The incidence in men and women is equal [5].

The histology of PV is an intra-epidermal vesicle with acantholysis [6]. The described antigens are desmoglein 1 (Dsg 1) and desmoglein 3 (Dsg 3) [7]. The immunopathology demonstrates deposition of autoantibodies on keratinocyte cell surfaces and their presence in patients' sera [8].

The mainstay of treatment of PV is systemic corticosteroids. Immunosuppressive agents (ISAs) are used for their steroid-sparing effect and possible ability to reduce autoantibody production [9–11]. Many patients do not respond to high dose long-term corticosteroids in combination with multiple ISAs. Newer methods of treatment, such as rituximab, have shown promise in such patients.

Rituximab is a chimeric monoclonal antibody that targets the CD20 molecule on B cells resulting in their lysis [12]. Pro-B cells, plasmablasts, and plasma cells do not express the CD20 molecule, and are unaffected by rituximab [12]. In 1997, the US Food and Drug Administration approved its use in lymphoma, in 2006 for rheumatoid arthritis (RA), in 2010 for chronic lymphocytic leukemia, and in 2011 for Wegener's granulomatosis [13]. Its use in PV is off label [14]. The rationale for the use of rituximab in patients with PV is based on its ability to deplete CD20+ B cells that presumably produce pathogenic antibodies [12].

The purpose of this review is to provide a critical analysis of the use of rituximab in the treatment of patients with PV.

METHODS

A PubMed search was conducted using the following keywords: pemphigus vulgaris, rituximab, anti-CD20 monoclonal antibody.

The patients included in this review were derived from studies published between 2000 and the present.

The following inclusion criteria were used: (1) English language; (2) clinical profile consistent with PV; (3) routine histology demonstrating suprabasilar cleft with acantholysis; (4) demonstration of intra-epidermal deposition of immunoreactants on perilesional skin processed by direct immunofluorescence; (5) whenever possible, information on treatments used concomitantly as well as after rituximab therapy; (6) information on dose and frequency of rituximab therapy; (7) provision of clinical outcomes at the end of the study period; (8) occurrence of relapses if they occur, and management of the relapse; (9) reporting the

length of follow-up; (10) documentation of serious adverse events, especially infections and mortality or lack thereof.

The information retrieved was categorized as follows: patient number, dose of rituximab and number of cycles, concomitant therapies, follow-up duration, adverse effects, clinical outcomes, relapses with re-treatments, levels of B cells, and autoantibody levels. The data are divided into case reports and case series. Case series included a minimum of six patients.

The patients were treated according to the lymphoma or RA protocol with rituximab. The lymphoma protocol consists of four weekly infusions of 375 mg/m^2 [14]. The RA protocol consists of two infusions of 1,000 mg 2 weeks apart [14].

Clinical outcomes of rituximab therapy included were used as described by Murrell et al. [15]. Complete remission on or off therapy was recorded as reported. In this analysis, partial responders were those patients in whom, after the initiation of rituximab therapy, the dose of systemic corticosteroids and immunosuppressive agents could be reduced by less than 50% compared to the prerituximab dose. Furthermore, in those patients, clinical disease occurred at intermittent periods, but did not require additional systemic therapy. Nonresponders were those patients who showed no clinical improvement and were considered treatment failures.

RESULTS

In 42 different publications, information on a total of 272 individual patients with PV treated with rituximab between 2000 and 2012 was available [16–57]. These data were divided into patients treated by (1) the lymphoma protocol, (2) the RA protocol, and (3) modifications or different combinations of either protocol. The information in each of the protocols was divided into case reports and case series.

In the lymphoma protocol, 22 case reports described 48 patients [16–37] and seven case series described 88 patients [43–49]. There are thus 136 patients who were treated by the lymphoma protocol.

There were no case reports in the RA protocol. Four case series described 75 patients [50–53].

Varying and modified versions of the RA or the lymphoma protocols were used within the same group of patients. Ten patients in five case reports got modified versions of the lymphoma protocol [38–42]. There were 51 patients in four different case series [54–57]. Therefore, when the case series and case reports are grouped together, 61 patients received the modified protocols.

The data on these different categories have been summarized in Table 1.

The Lymphoma Protocol

Case Reports

The clinical outcomes were as follows [16–37]: complete remission was observed in 32 (66.67%) patients; nine (18.75%) off therapy; 21 (43.75%) on therapy; and two (4.17%) with unclear treatment status. Nine (18.75%) were partial responders. Seven (14.58%) were nonresponders, one of whom after a second cycle had a complete response. The mean duration of follow-up was 12.91 months (range 1–36 months).

Concomitant therapies included: 10 (20.83%) patients on systemic corticosteroids alone [18, 20, 23, 30, 35, 36]; 36 (75%) patients on corticosteroids and ISAs [16, 17, 19, 21, 22, 24–26, 28, 29, 31–34, 37]. Two (4.17%) patients received rituximab as monotherapy [27].

Table 1 Summary of the data on the use of rituximab in the treatment of 272 patients with pemphigus vulgaris

	N	Concomitant therapy	Clinical outcome	Mean follow-up (range)	Relapse	SAE	Death	B cell levels	Antibody titers
Lymphoma protocol—case reports [16–37]	48	10 (20.83%) CS only 36 (75%) CS + ISAs 2 (41.7%) RTX only	9 (18.75%) CR off 21 (43.75%) CR on 2 (4.17%) CR NM 9 (18.75%) PR 7 (14.58%) NR	12.91 months (1–36)	6 patients (12.5%) after 8.73 months 1 patient had 2 relapses Retreated with: 1–RTX infusion 1–ISA 4–2nd RTX cycle	6 infections (12.5%) 2 LON (4.17%) 1 DVT + PE (2.08%)	1 (2.08%) from PCP 4 months after RTX 1 (2.08%) from septic shock 16 months after RTX	Time to depletion in 31 patients (64.58%): 1.76 months (range 0.25–7) Duration of depletion in 18 patients (37.5%): 12.84 months (range 2–23.6) Time to repopulation in 15 patients (31.25%): 12.43 months (range 5.5–23.6)	IIF: 4 No change, 2 ↑, 19 ↓ Dsg 3: 4 No change, 1 ↑, 25 ↓ Dsg 1: 6 No change, 1 ↑, 17 ↓
Lymphoma protocol—case series [43–49]	88	14 (15.9%) CS only 74 (84.1%) CS + ISAs	7 (8%) CR off, 34 (38.63%) CR on 15 (17%) CR NM 6 (6.82%) PR 26 (29.55%) clin rem NOS	21.74 months (10.8–41)	27 patients (30.7%) after 17.85 months Retreated with: 9–additional RTX cycles 3–2 infusions RTX at 1000mg 3 weeks apart 4–low-dose Prednisone 11–NM	1 infection (1.14%)	1 (1.14%) from septicemia 18 months after RTX	Reported in 35 patients (39.77%) Time to depletion: 0.25–1 month Duration of depletion: 12 months Time to repopulation: 18.93 months (range 12–34)	Dsg 3: 12 No change, 6 ↑, 66 ↓ Dsg 1: 4 No change, 2 ↑, 20 ↓
Rheumatoid arthritis protocol studies [50–53]	75	42 (56%) CS only 33 (44%) CS + ISAs	44 (58.67%) CR off 11 (14.67%) CR on 4 (5.23%) CR NM 15 (20%) PR 1 (1.33%) death	18.66 months (8.35–29)	28 (37.33%) patients after 18.25 months (range 4–41) 9 patients had 2 relapses 3 patients had 3 relapses Retreated with: 8–2nd RTX cycle 18–500mg RTX infusion/relapse 1–DM + RTX + IA 1–MMF	14 infection (18.67%)	1 (1.33%) from sepsis with *S. aureus*	Time to depletion in 62 (82.6%) patients: 1–4 weeks Time to repopulation in 42 (56%) patients: 6–14 months	IIF: 1 ↑, 2 ↓. Dsg 3 + Dsg 1: 66 ↓
Modified protocols—case reports [38–42]	10	2 (20%) CS only 7 (70%) CS + ISAs 1 (10%) NM	2 (20%) CR off 5 (50%) CR on 1 (10%) CR NM 2 (20%) PR	14.38 months (6–23)	NM	1 infection + PE (10%)	NM	NM	NM
Modified protocols—case series [54–57]	51	26 (51%) CS + ISAs 25 (49%) NM	7 (13.73%) CR off 5 (9.8%) CR on 22 (43.14%) CR NM 13 (25.49%) PR 4 (7.84%) NM	23.8 months (15.72–28.125)	18 (35.3%) patients after 18.75 months Retreated with: 9–2nd RTX cycle 1–minor therapy NOS 8–NM	1 LON (1.96%) 1 cardiac (1.96%)	1 (1.96%) from gastric perforation	Time to depletion in 18 (35.3%) patients: 1 week Duration of depletion in 7 (13.7%) patients: 23.5 months Time to repopulation in 11 (21.5%) patients: 23.8 months	Dsg 3 + Dsg 1: 33x ↓

clin rem NOS clinical remission not otherwise specified, *CR NM* complete remission therapy not mentioned, *CR off* complete remission off systemic therapy, *CR on* complete remission on systemic therapy, *CS* corticosteroids, *DM* dexamethasone, *Dsg 1* desmoglein 1, *Dsg 3* desmoglein 3, *DVT* deep vein thrombosis, *IA* immunoadsorption, *IIF* indirect immunofluorescence, *ISA* immunosuppressive therapy, *LON* late-onset neutropenia, *MMF* mycophenolate mofetil, *N* number of patients, *NM* none mentioned, *NR* nonresponder, *NOS* not otherwise specified, *PCP Pneumocystis carinii* pneumonia, *PE* pulmonary edema, *PR* partial remission, *RTX* rituximab, *SAE* serious adverse event

Six (12.5%) patients had seven relapses after a mean time of 8.73 months (range 1.5–12 months) after discontinuing rituximab [16, 22, 30, 31, 33]. One patient relapsed twice and received an infusion of rituximab each time. One patient received ISAs, while the remaining four patients received a second cycle of rituximab.

Serious adverse events reported included one death from *Pneumocystis carinii* pneumonia 4 months after rituximab [21], one death from septic shock after 16 months [36], one sepsis with multidrug-resistant *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Staphylococcus aureus* [16], one bacterial pneumonia [22], one recurrence of *P. aeruginosa* hip arthritis [22], one severe late-onset neutropenia after 27 weeks [28], one late-onset neutropenia and bacterial pneumonia after 19 weeks [29], one cytomegalovirus gastritis and retinitis [29], one deep vein thrombosis and pulmonary embolism [33], and one *P. carinii* pneumonia [33].

The time to depletion of B cells (undetectable levels in peripheral blood) after the first rituximab infusion was available for 31 (64.58%) patients and varied from 1 week to 7 months (mean 1.76 months) [16, 17, 20, 22–24, 26, 27, 29–31, 33, 35]. The mean duration of depletion of B cells was available for 18 (37.5%) patients and was 12.84 months (range 2–23.6 months) [16, 17, 20, 22, 24, 26, 27, 29, 33]. The mean time for repopulation of B cells (return to levels present in the peripheral blood before rituximab therapy) was available for 15 (31.25%) patients and was 12.43 months (range 5.5–23.6 months) [20, 22, 24, 26, 30, 31, 33].

Of the 15 (31.25%) patients reported with indirect immunofluorescence (IIF) only, two patients' titers remained unchanged throughout the study period, one of whom had two relapses [16, 17]. Two patients had an increase in their titers, one of whom relapsed as the titers increased while the other relapsed 5 months earlier than the increase [22]. Eleven patients had a decrease in titers at the end of the study period with no relapses reported [21–23, 29, 34]. In the 20 (41.67%) patients in whom enzyme-linked immunosorbent assay (ELISA) for Dsg 1 and Dsg 3 were performed, decreases in titers were observed with rituximab therapy and clinical response [26, 30, 31, 33, 35, 37]. A similar pattern was observed in 10 (20.83%) patients in whom both IIF and ELISA data were available [18, 20, 24, 25, 27, 32].

Case Series

Data on 88 patients were reported in seven case series [43–49]. Clinical response was as follows: complete response was observed in 56 (63.63%) patients; seven (8%) patients were off therapies; 34 (38.63%) patients were on therapy; and 15 (17%) patients had an unclear therapy status. Six (6.82%) patients had partial remission. Twenty-six (29.55%) patients improved but the definition of improvement was undefined. Nonresponders were not reported. The mean follow-up was 21.75 months (range 10.8–41 months).

Twenty-seven (30.68%) patients relapsed 29 times after a mean of 17.85 months (range 6–34 months) after discontinuation of rituximab [43, 45–49]. Nine of these patients were re-treated with additional rituximab cycles. Three patients were treated with two rituximab infusions 1,000 mg each, 3 weeks apart. Four patients received low-dose prednisone.

Serious adverse events included one death from septicemia after 18 months [43], and one pyelonephritis 12 months after discontinuation of rituximab [43].

Depletion of B cells was reported in 35 patients and occurred between 1 and 4 weeks,

and lasted up to 12 months [43–45]. Time for B cell repopulation occurred between 12 and 34 months (mean 18.93 months). The data suggest that the probability of relapse is higher in patients who take longer to repopulate.

In the majority of patients, a decrease in Dsg 3 titers was reported [43–49]. Nonetheless, 11 (12.5%) patients had persistently high titers while in clinical remission [43, 49]. Also, six patients who experienced a relapse at 12 and 18 months had increased titers at the time of relapse [48]. In 28 (31.8%) patients rituximab therapy resulted in a decrease in Dsg 1 antibody titers [43, 44, 47].

The Rheumatoid Arthritis Protocol

Case Series

Data on 75 patients were reported in four studies [50–53]. Complete remission was reported in 59 (78.67%) patients, of whom 44 (58.67%) were off therapy, 11 (14.67%) on therapy, and in four patients (5.33%) the therapy was unclear. Fifteen (20%) patients had partial remission, and one (1.33%) patient died. The mean duration of follow-up was 18.66 months (range 8.35–29 months).

Twenty-eight (37.33%) patients had 43 relapses [51–53]. Nine patients had two relapses. Three patients relapsed three times [53]. Relapses were treated with rituximab with success. In some patients, corticosteroids, ISAs, and immunoadsorption were used.

Adverse events occurred in 15 patients (20%) [50–53]. These included one death from sepsis with *S. aureus* [50]. Two other patients had sepsis [50, 51], one of whom had spinal hemorrhage with transient paraplegia of both legs, three had pneumonias [52, 53], six urinary tract infections [53], one extensive herpes simplex infection [51], one herpes keratitis [53], and one herpes zoster [53].

B cell levels were depleted within 1–4 weeks [51–53]. Approximately 80% of these were complete responders and 20% were partial responders.

IIF decreased in two patients studied [52]. In one patient, a relapse was accompanied by a rise in the titer [52]. ELISA levels decreased in some patients [50, 51, 53].

Modified Protocols

Case Reports

In ten patients, the modified lymphoma protocol was used [38–42]. Patients receiving modified lymphoma protocols received three or four additional monthly infusions and one received a complete second cycle of the protocol. Eight (80%) patients had complete remission, two (20%) had partial remission. None of the patients had relapses. Patients received corticosteroids or corticosteroids and ISAs as concomitant therapies. One patient experienced a bacterial pneumonia and pulmonary embolism [39].

B cell studies were not reported and antibody titers determined by IIF and ELISA decreased [38, 39, 41].

One study reported three patients treated with rituximab without details of the protocol [58]. They were not included in the analysis.

Case Series

Data on 51 patients were presented in four studies [54–57]. In the first study, six patients received eight weekly infusions of 375 mg/m^2 followed by a single dose once a month for 4 months [55]. All six had a complete remission off therapy. In 25 patients, two separate protocols were used [56]. One group received 375 mg/m^2 in two infusions in 2 weeks. Half of the patients had a complete remission and the other half had a partial remission. In the second

group, patients got three or more weekly infusions of 375 mg/m^2, and 90% had complete remission while 10% had partial remission. In the third study, 12 patients received the RA protocol at a dose of 500 mg at 2 week intervals [54]. Six of the 12 had complete remission off and on therapy, and six had partial remission. The fourth study concerned eight patients [57]. Of the four patients who got the RA protocol at a dose of 1,000 mg at 2 weeks, two had complete remission and two had partial remission. One patient received two infusions of 500 mg at 2 week intervals and had a complete remission. The remaining three patients received the lymphoma protocol, two had complete remission and one had a partial remission.

Among the 51 patients in the modified protocol group, 18 (35.3%) patients had relapses after a mean of 18.75 months (range 11.5–24.25 months) [54, 56, 57]. Half were treated with a second cycle of rituximab and experienced a complete remission [54, 57]. Serious adverse events were reported in three (5.8%) patients [54, 56]. One had gastric perforation resulting in death [56], one had cardiac complications [54], and one had sepsis with neutropenia 7.25 months later [54].

Depletion of B cells lasted up to 40 months in studies that reported it [54, 55]. In seven patients, repopulation was observed after 20–35 months. In five (71%) of these patients, repopulation was accompanied by relapses.

None of the studies reported IIF. ELISA for both Dsg 1 and Dsg 3 reported decreases [56, 57].

DISCUSSION

The analysis of the available literature on the use of rituximab in treating patients with PV is not only difficult but restrictive, as a direct consequence of the significant limitations of the data. Therefore, interpretation of the data analysis must be done in the light and perspective of these limitations. An obvious inference would be that such an analysis could be of limited value. On the contrary, these limitations are of significant benefit, because they will help in the design of future studies, and focus on elements of the pharmacodynamics of rituximab therapy.

Some of these limitations are as follows: the data come from multiple sources; there is a significant lack of uniformity in the selection of the patients, in defining their severity or extent of disease, and in identifying failed treatment before rituximab; the lack of an objective scoring system makes changes or responses difficult to evaluate numerically; the more concerning aspect is the limited follow-up provided by most authors, this becomes an important issue because significant side effects and relapses can occur several months after the discontinuation of rituximab therapy.

As rituximab is a B cell depletion therapy, many authors have not provided any data on B cell levels and the changes in autoantibody levels. None of the studies provide any rationale or scientific basis for the use of the lymphoma or RA protocols in treating patients with PV.

The response of patients to rituximab using the lymphoma protocol or RA protocol has been described in the results section. The total number of patients treated by the lymphoma protocol and its modification was 180. Ninety-two patients were treated with the RA protocol including its modifications. The length of follow-up for patients in the lymphoma protocol was a mean of 15.44 months (range 1–41 months) and 21.04 months (range 8.35–29 months) for the RA protocol. These figures permit preliminary conclusions. A complete remission occurred in

66.66% of patients on the lymphoma protocol and 75% in the RA protocol. This would suggest that both protocols are effective in producing clinical remissions during an 18-month follow-up. Using the lymphoma protocol during this period, 11.11% of these patients are off therapy and 33.33% are on therapy. In contrast, in the RA protocol, 53.26% are off therapy and 17.4% are on therapy. This apparent difference is partly due to the fact that the number of patients in whom the presence or absence of therapy while in complete remission is not mentioned in 22.22% of the patients in the lymphoma protocol, but only in 4.34% of the patients in the RA protocol. Interestingly, a partial response was observed in 12.78% of patients in the lymphoma protocol, but 23.91% of the patients in the RA protocol. Of significant interest is the fact that there were no nonresponders in patients treated with the RA protocol compared to 3.9% in the lymphoma protocol. The relapse rates were 22.78% in the lymphoma protocol and 35.87% in the RA protocol. The incidence of serious infections was 3.9% in the lymphoma protocol but 15.21% in the RA protocol. The mortality rate in the lymphoma protocol was 2.22% and 1.09% in the RA protocol. The difference between the two protocols in these important variables is striking and noteworthy. It is thus clear that there are significant and remarkable differences in the patient responses between the two protocols. The data analysis did not provide clear indications for specific reasons that may account for these differences.

Preliminary observations would suggest that while the use of the lymphoma protocol produces a lower response rate, there is a lower rate of recurrences and serious infections but a higher mortality rate. Patients treated by the RA protocol had higher response rates, a larger number of infections, but a lower mortality rate. This could be partly due to the fact that more patients were on corticosteroids and immunosuppressive agents as concomitant therapy in the lymphoma protocol, thus adding to the degree and duration of prolonged immune suppression.

To serve the best interests of the patient, it is useful and relevant to determine what purpose the lymphoma and RA protocols serve in their respective diseases. The use of rituximab in lymphoma patients has a duration of response of a median of 12 months (range 11–13.4 months) after which relapses frequently occur [59]. A median progression-free survival of 18 months and a 5-year relapse free survival of 28% was reported [59]. The most relevant use of rituximab comes from a 3-year progression-free survival study in which patients were given cyclophosphamide, doxorubicin, vincristine, and prednisone-like chemotherapy with or without rituximab and the 3-year survival rates were 93% and 84%, respectively [60]. Therefore, to obtain the benefit of rituximab in lymphoma patients, the addition of other chemotherapeutic agents is required, and can be best measured in 3-year survival rates.

The use of rituximab in RA is still a matter of debate and discussion. Between 2006 and 2011, 5,903 patients, who were reported in eight different trials, were treated [61–68]. These studies compared various parameters. The benefits of rituximab are measured by the American College of Rheumatology's 20%, 50% and 70% improvement criteria [61–68]. The only statistically significant dose regime was two cycles of 1,000 mg of rituximab over 48 weeks that achieved an American College of Rheumatology improvement of 20%. The Rituximab Consensus Expert Committee in 2011 stated that the optimal treatment paradigms have not yet been defined [69]. Recently, two extremely different treatment options have been suggested. In the treatment to target protocol, rituximab is given to keep the

disease activity score at 2.6 or less whether clinically needed or not. In the other protocol, rituximab is given on an as-needed basis [70]. Some patients need five cycles or more to maintain clinical remission [71–73]. However, at the present time, there is no protocol that provides prolonged and sustained remission in RA. Therefore, it is unclear how many cycles are required to keep patients symptom free, prevent joint destruction, or can be safely given in any defined period. Furthermore, RA patients usually receive rituximab with methotrexate concomitantly and often additional prednisone [61–68]. PV treated by the RA protocol needed multiple infusions to treat recurrent relapses [52, 53].

The objectives of treating patients with PV are different from those with lymphoma or RA. The optimal treatment for PV is one in which the disease is controlled, relapses are prevented, and the long-term sustained clinical remission without continued treatment can be achieved.

In patients with PV and ocular cicatricial pemphigoid, a defined protocol with a definitive endpoint was used [74, 75]. This combination of rituximab and intravenous immunoglobulin allowed for the discontinuation of previous systemic corticosteroids and ISAs and produced sustained clinical remissions. There were no infections or deaths.

There is a growing trend among dermatologists to use rituximab. Many variables have yet to be determined or defined. Providing guidelines or indications for therapy is preliminary and may change in the future. Presently, the indications for using rituximab could be as follows.

- Failure of conventional therapy for minimally 6 months.
- When conventional therapy has failed, or produced significant and catastrophic side effects, or is contraindicated, then intravenous immunoglobulin may be used [76].
- Active or latent infections are a definitive contraindication.
- Before initiating rituximab therapy, the goals and the endpoint should be discussed. The long-term side effects of rituximab in patients with PV are not yet known. Rituximab can result in cardiac side effects [77, 78]. Patients and their families should be advised of these facts.
- As clinical response may be faster with rituximab compared to conventional therapy, patients should be advised to return at frequent intervals for the early detection of possible recurrences and also for monitoring of late-onset side effects.

CONCLUSION

The use of rituximab in PV is an evolving work in progress. Although the data have limitations, the drug is effective in controlling recalcitrant disease. Whether this control is long term, life long, or of limited duration is not yet known. The data suggest that following either the lymphoma or RA protocols is not optimal or particularly advantageous, and modifications of both are warranted. Both carry a risk of severe and possibly fatal infections. Presently, it should be the treatment of last resort. Monitoring the levels of B cells (CD19+/CD20+) in the peripheral blood and immunoglobulin levels during and after therapy is advisable. A protocol that is unique for autoimmune mucocutaneous blistering disease is needed. Preliminary studies using such a protocol show promising results [74, 75]. Rituximab is the new frontier for the treatment of PV.

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