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Rituximab and intravenous immunoglobulin as alternatives to long-term systemic corticosteroids in the treatment of pemphigus: a single center case series of 63 patients

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Abstract

Rituximab and intravenous immunoglobulin [IVIg] have recently emerged as effective treatments for pemphigus refractory to corticosteroids [CS]. This case series sought to compare the clinical, serologic, and adverse effects of CS, IVIg, and rituximab in patients with pemphigus. A retrospective review of 63 patients with pemphigus vulgaris (PV), pemphigus foliaceus (PF), or paraneoplastic pemphigus (PNP) was performed. Clinical remission (CR), serologic remission (SR), and adverse effects were evaluated. Three study groups were compared: patients treated with systemic CS, refractory patients treated with IVIg, and refractory patients treated with rituximab. The overall number of adverse effects was not significantly different between the groups but those observed in patients treated with systemic CS were more severe. CR was less likely in the patients treated with systemic CS than in patients treated with IVIg or rituximab, P-value = 0.000467. SR was more likely in patients treated with systemic CS or rituximab than in patients treated with IVIg, P-value = 0.002118. These results suggest that the clinical efficacy of IVIg is not correlated with an expected concomitant SR. Frequently reserved for refractory pemphigus, IVIg and rituximab are significantly more likely to produce clinical remission than systemic CS therapy, suggesting their utility as first-line treatments.

Keywords: rituximab, intravenous immunoglobulin, corticosteroids, pemphigus foliaceus, pemphigus vulgaris

Introduction

Pemphigus vulgaris (PV) is the most common subtype of pemphigus and is characterized by suprabasal acantholysis that produces painful mucocutaneous blisters and erosions [1]. Pathogenic autoantibodies of the IgG subset are directed against desmoglein 3 (DSG3) and desmoglein 1 (DSG1), or DSG3 alone. Patients with pemphigus foliaceus (PF) produce only anti-DSG1 and present with subcorneal or intragranular cutaneous blisters and erosions, which can mimic papulosquamous eruptions [2]. Paraneoplastic pemphigus (PNP) is characterized by autoantibodies against DSG1, DSG3, and the intracellular plakin family of proteins. [3]. Enzyme-linked immunosorbent assay (ELISA) is the most accurate diagnostic method overall for PV and PF, with ≥ 96% sensitivity and ≥ 98% specificity [4]. In all variants of pemphigus, titers of pathogenic autoantibodies correlate with disease activity [5]. ELISA values correlate better with disease activity than indirect immunoflurorescence (IIF) and are superior to direct immunofluorescence (DIF) in confirming disease remission [4].

The side effects of long-term systemic corticosteroid (CS) use are well-documented, such as frequent infections, high blood glucose, cognitive dysfunction, and weight gain [6]. Additionally, there is no consensus on recommended maintenance dosing, especially with the adjunct use of steroid-sparing agents such as mycophenolate mofetil (MMF) and azathioprine (AZA), [7]. Because of its mild adverse effects and steroid-sparing utility, intravenous immunoglobulin (IVIg) is considered to be an effective second-line

treatment for refractory pemphigus [11]. Rituximab, a monoclonal anti-CD20 antibody, has achieved complete remission (CR) or partial remission (PR) in pemphigus in several observational studies with minimal side effects [8, 9].

We report the clinical experience from a single institution in a series of 45 patients with PV, 17 patients with PF, and one patient with PNP. Of patients with PV, 21 were refractory to CS and steroid-sparing agents and initiated treatment with IVIg. Of those 21 patients with PV on IVIg, 9 patients ultimately underwent therapy with rituximab. There were only 3 patients with PF who initiated treatment with IVIg, and 2 of these 3 patients ultimately required rituximab.

Methods

Following approval by the institutional review board, patients were retrospectively identified from an electronic search of the medical diagnosis "pemphigus" using the electronic medical record database software. All patients were treated by one of the authors (SH) at Baylor College of Medicine between April, 2010 and December, 2016. The diagnoses of PF and PV were confirmed by histopathology and DIF. For two patients with PF and for 10 patients with PV, ELISAs for anti-DSG1 and anti-DSG3 were also performed for diagnosis and to monitor disease activity. Diagnosis of PNP was supported by histopathology, DIF, IIF on rat bladder, immunoblot for envoplakin and periplakin, and ultimately, identification of an underlying neoplasm – extranodal follicular dendritic cell sarcoma.

Treatment with systemic CS, IVIg, or rituximab was based on disease severity, response to other treatments, and patient preference, following a detailed discussion of potential adverse effects and available evidence of efficacy. Dosing of CS (oral prednisone) was initiated at 1 mg/kg/daily, was continued until remission and was then tapered down to the lowest dosage that controlled the disease. IVIg was dosed as following: 2 grams for every kilogram bodyweight, infused over the course of 4 or 5 days monthly. Rituximab infusions were administered at a dose of 1g/kg on days 1 and 15 of a single treatment cycle, which was repeated as necessary once every 6 months.

Table 1. *Characteristics of patients with pemphigus in a single center series. N: number, Y: years, PV: pemphigus vulgaris, PF: pemphigus foliaceus, PNP: paraneoplastic pemphigus.*

Characteristic	Patients (N = 63)
Male gender (N)	31
Age at first visit (Y)	
Median	49
Range	19 - 82
PV	45
Male gender (N)	21
Age at first visit (Y)	
Median	45
Range	19 - 69
PF (N)	17
Male gender (N)	10
Age at first visit (Y)	
Median	64
Range	34 - 82
PNP (N)	1
Male gender (N)	0
Age at first visit (Y)	50

Data extracted from the chart review included age at first visit, gender, clinical presentation, diagnostic methods, treatment regimens and therapeutic response, adverse effects, date of first and last clinical encounter, and serologic indices from available ELISA studies.

Disease was considered refractory in patients for whom discontinuation of CS therapy, with or without the concomitant steroid-sparing agents AZA or MMF, was not possible without subsequent flare. For patients with refractory disease, treatment with IVIg with or without subsequent rituximab was elected. The time to remission was also compared. In evaluating remission status, CR was defined as lack of new blisters for 6 weeks whereas PR was defined as minimal lesions (1 to 2, infrequent, small blisters) over the course of 6 weeks.

Case series with description of treatment response

Table 2: *Response to therapy and adverse effects in patients with PF treated with CS.*

CS use (N)	Remission after CS (N)	Adverse effects (N)	Additional required treatment(s) (N)	Notes
Topical (5)	4	None	IVIg (1)	Two patients used topical CS, due to intolerance for oral CS
ST-CS (6)	6	None	None	
LT-CS (6)	2	HTN (6) NIDDM (2) Weight gain (3) Cataracts (1) Insomnia (1)	MMF (2) Rituximab (1) Refractory to all treatments (1)*	*One patient was not responsive to CS, steroid-sparing agents, or IVIg, and infusion reaction to rituximab, prevented completion of that therapy.

and adverse effects were produced for the following two cohorts: patients with PF treated with CS (with or without adjunctive steroid-sparing agents) and patients with PV treated with CS (with or without adjunctive steroid-sparing agents). Case series with description of treatment response, adverse effects, and serologic indices (ELISA values) were produced for patients with refractory PF or PV who were treated with IVIg with or without subsequent rituximab. Finally, patients with available serologic data were separated into 3 broad categories for comparison: patients treated with systemic CS with or without the addition of a steroid-sparing agent (CS group), patients with refractory disease treated with IVIg but not rituximab (IVIg group), and patients with refractory disease treated with rituximab following IVIg (rituximab group). Data analysis for this comparison was completed at the University of Florida (software: R programming version 3.4.0) with a 3-sample test for equality of proportions without continuity correction to generate P-values; where a statistically significant P-value (< 0.05) was identified, 95% confidence intervals were created.

Results

Sixty-three patients meeting inclusion criteria were identified: 45 with PV, 17 with PF, and one with PNP. Patient demographics are summarized in **Table 1**. Given that disease resolution was observed in the single patient with PNP following surgery and radiation therapy for an underlying sarcoma, this treatment response will not be discussed further.

Among the 17 patients with PF, there were three patterns of CS therapy: topical CS, systemic CS (oral prednisone) for flares only (ST-CS), and continuous systemic CS (oral prednisone, LT-CS) for maintenance of disease control. **Table 2** summarizes the treatment responses and adverse effects in patients with PF treated with CS. Only two patients (33%) were able to control their disease. Although topical CS and ST-CS were not associated with significant adverse effects, all 6 patients on LT-CS therapy (with or without the addition of MMF) developed or experienced an exacerbation of hypertension (HTN), two patients developed non-insulin dependent diabetes (NIDDM), and 3 patients had significant weight gain; other reported adverse effects included cataracts and insomnia.

Among the 45 patients with PV, there were 5 patterns of CS therapy: topical CS only, ST-CS, and patients who took low (2.5 mg to 20 mg per day), medium (21 mg to 40 mg per day), or high (40-80 mg per day) doses of systemic CS (oral prednisone) continuously (low, medium, or high dose LT-CS). **Table 3** summarizes the treatment responses and adverse effects in patients with PV treated with CS. The patients who were able to control their disease with topical CS reported no adverse effects. Among patients with PV who had longer flares undergoing ST-CS, 7 of 9 patients were able to manage flares with oral prednisone with or without a steroid-sparing agent (MMF). However, the average daily dose of prednisone was 60 mg, and side effects were significant, including weight gain. Among the patients with PV undergoing low dose LT-CS, 8 of 16 patients (50%) were able to manage their disease state with prednisone with or without the addition of a steroid-sparing agent. (2 MMF, 1 AZA); adverse effects included weight gain (n = 3, with one patient gaining 100 pounds in one year), NIDDM, osteoporosis, frequent infections, and steroid acne. In patients with PV and medium dose LT-CS, 23% (n = 3) were able to manage their condition with CS

Table 3. *Response to therapy and adverse effects in patients with PV treated with CS.*

CS use (N)	Response to CS (N)	Adverse effects (N)	Additional required treatment(s) (N)	Notes
Topical (3)	None	None	MMF (1)	
ST-CS (9)	Refractory (2) Remission - monotherapy (2) Remission with MMF (5)	Weight gain (3) Steroid acne (1)	IVIg (2)	
Low dose LT-CS (16)	Refractory (8) Remission - monotherapy (5) Remission with MMF (2) Remission with AZA (1)	Weight gain (3) NIDDM (1) Osteoporosis (1) Frequent infections (1) Steroid acne (1)	IVIg (4) Rituximab (3) Refractory with MMF (1)	One patient experienced weight gain of 100 pounds in 1 year. Three of 4 patients later achieved remission with IVIg. Three of 3 patients achieved remission with rituximab.
Medium dose LT-CS (13)	Refractory (10) Remission-monotherapy (3)	HTN (3) Osteoporosis (2) Weight gain (2) Frequent Infections (1) Mood changes (1) NIDDM (1)	IVIg (5) Rituximab (2) Refractory with MMF (1) Refractory with AZA (2)	All patients treated with IVIg and/or rituximab later achieved remission were able to discontinue CS therapy.
High dose LT-CS (4)	Refractory (3) Remission-monotherapy (1)	Weight gain (4) NIDDM (2) HTN (1) Early menopause (1) Osteoporosis (1)	IVIg (1) Rituximab (2)	All patients treated with IVIg and/or rituximab later achieved remission were able to discontinue CS therapy.

monotherapy. Medium dose LT-CS was associated with HTN, osteoporosis, weight gain, frequent infections, mood alterations, and NIDDM. Finally, in the cohort of 4 patients with PV who underwent high dose LT-CS (with or without the addition of MMF), one patient achieved CR; however, the mean weight gain was 48 pounds within one year, two patients developed NIDDM, and one patient developed HTN.

Of the patients with refractory PV or PF (n=23), all received IVIg, and 15 of these patients received IVIg without ultimately requiring rituximab; 14 patients achieved CR or PR after an average duration of 3.8 months. Four of the 23 patients who received IVIG treatment reported headaches following infusion; only in one patient were headaches severe enough to limit occupational activity. Eleven patients subsequently underwent rituximab therapy: all 8 patients who completed at least one cycle of rituximab therapy achieved CR following an average duration of 10.5 months. Three of these 11 patients experienced infusion reactions that precluded completion of a single treatment cycle. **Table 4** summarizes the clinical characteristics, therapeutic response, adverse effects and serologic data for patients treated with IVIg and rituximab.

Serologic indices demonstrated discordance between clinical response to therapy and levels of pathogenic autoantibodies among patients who achieved PR or CR with IVIg without subsequent rituximab: among 9 patients with ELISA indices, 7 demonstrated high anti-DSG levels, 1 demonstrated intermediate levels, and 1 patient had low levels. This discordance between serology and therapeutic response was not observed in rituximab-treated patients: the 3 patients who achieved CR with rituximab therapy and for whom ELISA indices were available demonstrated drastic reductions in pathogenic autoantibody levels. **Figure 1** provides a logarithmic summary of the serologic data from patients treated with IVIg and rituximab over time following therapy.

Among the 3 broad treatment categories for comparison (CS group, IVIg group, and rituximab group), a 3-sample t-test without continuity correction found that CR was significantly less likely in the CS group that in the IVIg or rituximab groups (p-value = 0.000467). SR was significantly more likely in the CS or rituximab groups than in patients treated

Table 4: *Clinical characteristics, response to therapy, adverse effects, and serologic data in patients with PV and PF treated with IVIg and/or rituximab.*

Patient	Gender	Age	Diagnosis	Response to IVIg and adverse effects	Response to rituximab and adverse effects	Serologic data
1	Female	54	PF	Clinical improvement after 3 months	-	Baseline: ELISA anti-DSG1 = 5 U, anti-DSG3 = 1 U; positive IIF titer against MES One year: ELISA anti-DSG1 =4 U, anti-DSG3 = 1 U; positive IIF titer against MES
2	Male	34	PF	Failed to enter remission after 1 year	Remission after 2 Years	N/A
3	Male	35	PF	CR	Infusion reaction	After treatment: ELISA anti-DSG1 = 224 U
4	Male	24	PV	Ineffective as monotherapy for mucosal lesions after 3 months	With adjunct IVIg, entered remission after 6 months and discontinued treatment aafter 1 year	Baseline: ELISA anti-DSG1 = 81 U, anti-DSG3 = 260 U Six months after rituximab: ELISA anti-DSG1 = 67 U, anti-DSG3 = 78 U Thirteen months after rituximab: ELISA anti-DSG1 = 2 U, Anti-DSG3 = 5 U
5	Male	50	PV	Discontinued after 1 year due to lack of efficacy for mucosal lesions	Remission after 1 cycle	Baseline: ELISA anti-DSG1 = 1 U, anti-DSG3 = 27 U After rituximab: ELISA anti-DSG1 = 1 U, anti-DSG3 = 3 units
6	Female	48	PV	Remission after 2 cycles	-	N/A
7	Male	27	PV	PR with infrequent mild flares	-	N/A
8	Male	19	PV	PR after 2 months but then ineffective at 2 years	Remission after 1 year (2 cycles)	N/A
9	Female	57	PV	CR after 8 months	-	N/A
10	Female	50	PV	Remission after 3 months then maintenance cycles	-	Baseline ELISA anti-DSG1 = 660 U; Anti-DSG3 = 880 U Five months after IVIg: anti-DSG1 = 11 U, anti-DSG3: 122 U
11	Male	28	PV	Effective after 4 months, but discontinued due to time constraints	Remission 6 months after treatment	N/A
12	Female	55	PV	One cycle administered for severe symptoms, no remission	-	N/A

Patient	Gender	Age	Diagnosis	Response to IVIg and adverse effects	Response to rituximab and adverse effects	Serologic data
13	Male	65	PV	Improved after 3 months, PR at 6 months, then maintenance cycles	-	Baseline: ELISA anti-DSG1 = 22 U, anti-DSG3 = 570 U Three months after IVIg: ELISA anti-DSG1 = 17 U, anti-DSG3 = 120 U Six months after IVIg: ELISA anti-DSG1 = 14 units, anti-DSG3 = 310 U
14	Male	37	PV	Improved after 4 monthly cycles followed by infrequent maintenance cycles	-	Baseline: ELISA anti-DSG1 = 4 U, anti-DSG3 = 11 U; positive IIF against MES, negative IIF against HSS Four months after IVIg: ELISA anti-DSG1 = 13 U, anti-DSG3 = 17 U; negative IIF against MES and HSS
15	Male	29	PV	Improved but discontinued following deep vein thrombosis	Remission after therapy	N/A
16	Female	35	PV	CR after 3 months	-	Baseline: ELISA anti-DSG3 = 168 units Three months after IVIg: ELISA anti-DSG1 = 14 U, anti-DSG3 = 1740 U
17	Male	53	PV	Improved after 3 months then CR; at 3 years, infrequent maintenance cycles	-	Baseline: ELISA anti-DSG1 = 33 U, anti-DSG3 = 480 U One year after IVIg: ELISA anti-DSG1 = 52 U, anti-DSG3 = 630 U Two years after IVIg: ELISA anti-DSG1 = 70 U, anti-DSG3 = 980 U Three years after IVIg: ELISA anti-DSG1 = 94 U, anti-DSG3 = 840 U
18	Female	65	PV	Significant improvement after 2 months	-	N/A
19	Female	39	PV	PR and discontinued treatment after 2 years PR maintained after 4 years without therapy	Infusion reaction	Baseline: ELISA anti-DSG1 = 36 U, anti-DSG3 = 173 U Two years after IVIg: ELISA anti-DSG1 = 3 U, anti-DSG3 = 150 U Four years after IVIg (no treatment): ELISA anti-DSG1 = 2 units, anti-DSG3 = 475 U
20	Male	35	PV	PR after 4 months	-	Baseline: ELISA anti-DSG1 = 2 U, anti-DSG3 = 90 U Two months after IVIg: ELISA anti-DSG1 = 2 U, anti-DSG3 = 65 U Ten months after IVIg: ELISA anti-DSG1 = 11 U, anti-DSG3 = 420 U

Patient	Gender	Age	Diagnosis	Response to IVIg and adverse effects	Response to rituximab and adverse effects	Serologic data
21	Male	43	PV	Minimal improvement after 4 months	Remission after 1 year	Baseline: ELISA anti-DSG1 = 0 U, anti-DSG3 = 171 U Three months after IVIg: ELISA anti-DSG1 = 0 U, anti-DSG3 = 60 U Three months after rituximab: ELISA anti-DSG1 = 0 U, anti-DSG3 = 16 U
22	Male	27	PV	Sustained improvement over 1 year	Infusion reaction	N/A
23	Female	48	PV	Loss of efficacy after 13 months Infrequent maintenance cycles after treatment with rituximab	Remission after 1 year Relapse 1 year later; re-entered remission after additional cycle	N/A

with IVIg (p –value = 0.002118). However, the overall number of adverse effects was not significantly different between the 3 groups (p-value = 0.1887). **Table 5** summarizes the comparison of these 3 broad treatment categories.

Case Discussion

Owing to the rarity of this group of diseases and the lack of randomized controlled data, treatment for pemphigus largely depends on observational studies. To our knowledge, this retrospective study represents the largest reported series of patients with pemphigus from a single institution, treated by a single clinician. Treatment regimens varied depending on the severity of disease and response (or lack thereof) to initial CS therapy. Patients who elected IVIg or, ultimately, rituximab either demonstrated disease refractory to CS, with or without steroid-sparing effects of MMF or AZA, or significant to severe adverse effects of CS therapy.

Adverse effects reported in the patients who underwent LT-CS therapy are well-described in previous studies [6, 10]. Established effects related to chronic systemic CS therapy include osteoporosis, hyperglycemia, weight gain, and susceptibility to infection, amongst others. In this series of patients, weight gain related to LT-CS (and ST-CS in patients with PV) posed the greatest concern to patients. A descriptive study found new-onset hyperglycemia in 40% of patients who received systemic CS for the treatment of pemphigus [11]. Thirty-three percent of patients with PF and 12% of patients with PV undergoing LT-CS

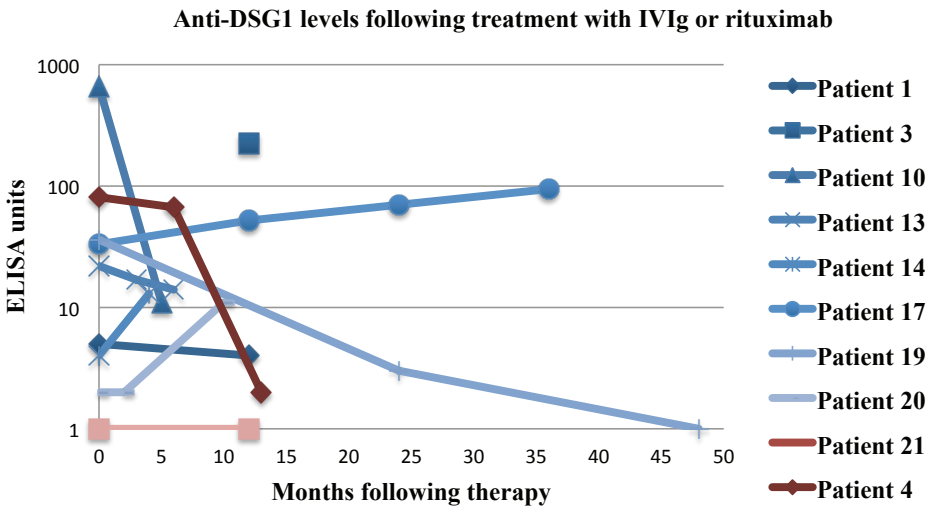

Figure 1: *Levels of pathogenic autoantibodies, determined by ELISA, in patients with PF and PV following treatment with IVIg or rituximab. Rituximab-treated patients are represented in red while patients treated with IVIg without rituximab are represented in blue. Patient numbers listed in* **Table 4** *are indicated to the right of their series. Patients 3 and 23 only had post-treatment data and were included in the graph to demonstrate their respective trends. Patients 1 and 3 had PF and thus do not have anti-DSG3 values on the graph. DSG1- desmoglein 1; DSG3- desmoglein 3; IVIg- intravenous immunoglobulin; ELISA-enzyme-linked immunosorbent assay; PF- pemphigus foliaceus; PV-pemphigus vulgaris.*

Table 5. *Comparison of 3 broad treatment categories in clinical remission, serologic remission, and adverse events.*

Group	Number	Clinical Remission	Serological Remission	Adverse Events
Steroids	33	15	6 out of 6	15
IVIg	15	14	2 out of 9	10
Rituximab	8	8	4 out of 4	6

therapy developed NIDDM. The incidence of these significant adverse effects prompts the use of less toxic treatment regimens for pemphigus.

IVIg suppresses pathogenic antibody production by B cells, neutralizes complement components, blocks autoantibody-receptor interactions, prevents T-cell activation by autoantibodies, and interferes with migration of inflammatory cells into target tissues. IVIg does not suppress the host immune system [12-18]. Adverse reactions to IVIg include mild transient reactions, such as chills, myalgia, headaches, back pain, and increase in blood pressure, occurring in 10-30% of infusions. These infusion reactions can be reduced with a slower infusion rate [19]. The clinical efficacy of IVIg for pemphigus was correlated with a concomitant decrease in anti-DSG levels in previous controlled studies [27-29]. However, in this study, concordance between serologic and clinical response to IVIg was not observed; in IVIG-treated patients with CR and PR, autoantibody levels remained elevated. A likely explanation for this difference is that ELISA was performed months to years following the final treatment cycle, rather than 2 weeks following treatment as in previous studies. Our study aligned with previous data suggesting a steroid-sparing effect of IVIg; all IVIg-treated patients in this series were able to taper or discontinue systemic CS [20].

Rituximab is a chimeric monoclonal antibody that targets the CD20 ligand on B lymphocytes, inducing depletion of B cells within 2 to 3 weeks of initial treatment. It is approved by the Food and Drug Administration for the treatment of NHL and rheumatoid arthritis. CD20-negative plasma cells, which produce antimicrobial antibodies, are located in the bone marrow and are not affected by rituximab. CD20-positive, short-lived plasma cells found outside of the bone marrow are targeted by rituximab, explaining the drug's ability to decrease pathogenic autoantibodies without affecting protective (antimicrobial) immunoglobulin [21]. Several studies have described the successful use of rituximab and IVIg as first-line treatments in PV to obtain a prolonged, sustained clinical remission in 95% of patients with severe or refactory pemphigus, with a delayed response following a duration of 3 months to 1 year. Combination therapy with IVIg is also effective and produces sustained SR [22]. Similarly, in this study rituximab treatment was highly effective and correlated with SR. Infusion reaction is a common side effect of rituximab related to its chimeric structure and was the only adverse effect in this study. Infrequently reported adverse effects include sustained hypogammaglobulinemia, deep vein thrombosis, and neutropenia [23].

Among the 3 broad treatment categories for comparison (CS goup, IVIg, and rituximab groups), clinical remission was significantly less likely in the CS group than in the IVIg or rituximab groups. SR was significantly more likely in the CS or rituximab groups than in patients treated with IVIg. These findings are consistent with the clinical experience in this series of patients and further support the use of IVIg and rituximab in refractory disease. Although the overall number of adverse effects was not statistically different between the 3 groups, the adverse effects observed in the CS group were considerably more severe and clinically significant — including weight gain, hypertension (HTN), and non-insulin dependent diabetes (NIDDM) — than those attributed to IVIg. Notably, this study and these comparisons are limited by small sample sizes. Additionally, given that this these findings represent a retrospective review of medical charts, it is possible that some significant adverse effects attributable to these treatment regimens were not recorded and therefore not captured in the study.

Conclusion

For patients with pemphigus who are unable to

achieve disease remission with CS or in whom significant adverse effects due to CS therapy occur, IVIg and rituximab are more effective and better-tolerated therapies. Many patients in this series, the largest single-center series of patients treated by a single clinician, were able to achieve CR with total cessation of therapy or with infrequent maintenance treatment with these drugs. Additionally, the potentially serious adverse effects of systemic CS, such as HTN, infections, marked weight gain, and NIDDM, were not observed with IVIg or rituximab. In this series and in several previous studies, IVIg and rituximab have been used successfully in patients with pemphigus refractory to CS therapy. Of note, levels of pathogenic autoantibodies reflect clinical response to treatment rituximab, but not with IVIg. Financial constraints and denial of insurance coverage have also limited the use of these agents. However, given their superior efficacy and adverse effect profile compared to systemic CS, clinicians should consider IVIg and rituximab in refractory disease, and even as first-line agents. Future research, particularly randomized controlled trials, demonstrating the use of IVIg and rituximab in this context, would be valuable for patients with pemphigus.

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