

ORIGINAL ARTICLES

Prolonged Complete Clinical Remission in Patients With Severe Pemphigus Vulgaris After Cycles of Intravenous Cyclophosphamide

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Abstract. *Background.* Corticosteroids are the systemic treatment of choice in patients with pemphigus vulgaris, but chronic administration is associated with side effects. Intravenous treatment with cyclophosphamide can improve the clinical signs of pemphigus vulgaris.

Material and methods. We prospectively studied 8 patients diagnosed with pemphigus vulgaris. Six of these had mucocutaneous pemphigus vulgaris and 2 had mucosal pemphigus vulgaris. Treatment consisted of 10 cycles of cyclophosphamide at a dose of 10-15 mg/kg separated by 15 days, while maintaining the initial corticosteroid and immunosuppressant dose. Clinical efficacy was assessed and the anti-epidermal intercellular substance (EIS) and anti-desmoglein (DSG) 3 and 1 antibody titers were monitored (by indirect immunofluorescence and enzyme-linked immunosorbent assay, respectively).

Results. All patients with pemphigus vulgaris responded excellently to treatment. Five of the 8 patients achieved complete remission of pemphigus lesions after 10 cycles of cyclophosphamide. In the other 3 patients, the skin lesions disappeared a few weeks after the last cycle of cyclophosphamide. A substantial reduction in immunosuppressant dose was possible in all patients. Furthermore, an improved immunologic response was observed in all cases after cyclophosphamide treatment, with decreased anti-DSG1 and anti-DSG3 antibody titers and well as decreased circulating anti-EIS antibody titers. During the mean 15.1 month follow-up (range, 1-25 months), no new lesions appeared and no side effects of cyclophosphamide therapy were reported.

Conclusions. Fortnightly cycles of intravenous cyclophosphamide may be a useful therapeutic option in patients with severe pemphigus vulgaris. A reduction of corticosteroid dose was possible with this therapeutic approach and the cumulative cyclophosphamide dose was lower than with daily oral administration. Our findings also show that the therapeutic approach induces clinical and immunologic remission in most patients.

Key words: autoantibodies, cyclophosphamide, desmoglein, immunosuppressants, pemphigus vulgaris.

REMISIÓN CLÍNICA COMPLETA PROLONGADA EN PACIENTES CON PÉNFIGO VULGAR GRAVE DESPUÉS DEL TRATAMIENTO CON CICLOS INTRAVENOSOS DE CICLOFOSFAMIDA

Resumen. *Introducción.* Los corticosteroides son el tratamiento sistémico de elección en los pacientes con pénfigo vulgar (PV). Su administración crónica produce efectos secundarios. La administración de ciclofosfamida (CF) intravenosa puede mejorar las manifestaciones clínicas del PV.

Material y método. Estudiamos prospectivamente 8 pacientes diagnosticados de PV. Seis de los pacientes presentaban PV cutáneo-mucoso (PVCMM) y 2 casos PV mucoso (PVM). El tratamiento consistió en 10 ciclos quincenales de CF en dosis de 10-15 mg/kg, manteniendo la dosis inicial de corticosteroides y de inmunosupresor. Se evaluó la eficacia clínica y la evolución del título de anticuerpos anti-sustancia intercelular epidérmica (SIE) (inmunofluorescencia indirecta) y específicamente anti-desmogleína (Dsg) 1 y 3 (ELISA).

Resultados. Todos los pacientes con PV presentaron una excelente respuesta al tratamiento. Cinco de los 8 pacientes presentaron una remisión completa de las lesiones de PV después de los 10 ciclos de CF. En los otros 3 pacientes las lesiones cutáneas desaparecieron unas semanas después del último ciclo de CF. En todos los pacientes se redujo de forma importante la dosis de inmunosupresores. Además, en todos los casos se observó una mejoría en la respuesta

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inmunológica después del tratamiento con CF, con disminución en el título de anticuerpos frente a las Dsg 1 y 3, así como del título de anticuerpos circulantes frente a la SIE. Tras un seguimiento medio de 15,1 meses (1-25 meses) ningún paciente ha presentado nuevas lesiones de PV. A su vez, no se han observado efectos secundarios por la CF.

Conclusiones. La administración de pulsos quincenales de CF intravenosa puede ser una opción terapéutica útil en pacientes con PV grave. Este esquema terapéutico permite disminuir la dosis de corticosteroides con una menor dosis acumulada de CF que en la administración oral diaria. Además, nuestros resultados muestran que este esquema terapéutico se acompaña de una remisión clínica e inmunológica en la mayoría de los pacientes.

Palabras clave: autoanticuerpos, ciclofosfamida, desmogleína, fármacos inmunosupresores, pénfigo vulgar.

Introduction

Pemphigus vulgaris (PV) is an autoimmune blistering disease mediated by immunoglobulin (Ig) G-type autoantibodies directed against desmogleins (Dsg) in the dermosomes of skin and mucosal keratinocytes.¹ There are 2 clinical variants of the disease: mucocutaneous PV and mucosal PV. Mortality from PV, which is currently estimated at between 5% and 15%,² was high until systemic corticosteroid therapy became the treatment of choice. In many patients, the cause of death is associated with adverse reactions related to the long-term administration of corticosteroids rather than with PV itself.³⁻⁵

PV can be treated effectively with a wide range of drugs, which also serve to reduce the cumulative corticosteroid dose. Noteworthy among these drugs are antiinflammatories, immunomodulators, and immunosuppressants such as azathioprine, mycophenolate mofetil, cyclosporin, and cyclophosphamide. The combined use of corticosteroids and immunosuppressants has reduced both the morbidity and mortality associated with PV.^{5,6}

The main treatment goal in patients with PV is to achieve optimum clinical outcomes with minimum morbidity. Numerous studies have demonstrated the clinical efficacy of intravenous pulse cyclophosphamide therapy.⁷⁻¹¹ This route of administration has proven to be as efficacious as the administration of oral cyclophosphamide on a daily basis but it has the added advantage that it is associated with lower morbidity.^{12,13} Following recommendations in the literature on the administration of intravenous pulse cyclophosphamide therapy,^{10,11} we treated 8 patients, all with severe PV, with 2-weekly cycles of cyclophosphamide. The patients had all received previous treatment with oral prednisone and azathioprine or mycophenolate mofetil. The primary aim of this study was to evaluate the clinical and immunologic efficacy of intravenous cyclophosphamide administered every 2 weeks and to determine how this treatment regimen might help to reduce the use of corticosteroids and immunosuppressants.

Patients and Methods

We performed a prospective study of 8 patients diagnosed with severe PV between 2002 and 2007 at the dermatology department at the Clínica Universitaria de Navarra in Pamplona, Spain. Diagnosis was based on the analysis of biopsy specimens from active lesions, results from direct immunofluorescence studies of perilesional skin, detection of circulating of antibodies directed against Dsg1 and Dsg3 by enzyme-linked immunosorbent assay (ELISA) (MBL Naka-Ku, Nagoya, Japan), and epidermal intercellular substance (EIS) by indirect immunofluorescence (Movaco-Grifols, Barcelona, Spain). The clinical and epidemiologic characteristics of all the patients are shown in Table 1. Six of the patients had mucocutaneous PV and 2 had mucous PV.

Included in the protocol were patients with moderate or severe PV according to the scale proposed by Fleischli et al,¹¹ patients with flare-ups or old lesions that were not healing despite adequate treatment, and patients with adverse reactions to high-dose prednisone used to control PV lesions. The patients had received the following immunosuppressants prior to inclusion in the study: anti-CD20 monoclonal antibody, plasmapheresis, methotrexate, intravenous Ig, and oral cyclophosphamide (Table 1).

Although we started by administering intravenous cyclophosphamide as monthly pulses, as is recommended in the literature,⁸ we decided to shorten this interval to 2 weeks when our first patient developed a flare of disease activity before the second infusion was due (at 4 weeks). This first patient received 10 cycles, as did the other patients but at 2-weekly intervals.

Exclusion criteria were pregnancy, breast-feeding, administration of cytotoxic drugs in the preceding month, signs of severe infection, history of neoplastic disease, consumption of considerable amounts of alcohol or toxic substances, presence of active peptic ulcer, history of liver dysfunction (alanine aminotransferase, >70 U/L), kidney dysfunction (serum creatinine, >1.5 mg/dL), or heart failure (New York Heart Association class III or IV), and a leukocyte count of under 2000/ μ L. Clinical and

Table 1. Clinical Data for Patients With Pemphigus Vulgaris (PV) Before Treatment With Pulse Intravenous Cyclophosphamide (Cy) Therapy Every 2 Weeks

Patients	Sex/Age, Type of PV	Previous Treatments	Adverse Reactions Due to Prednisone	Disease Activity ^a	Time Since Clinical Onset
1	M/54 MC/MU	P-Az	None	MC, severe; MU, severe	6 mo
2	F/40 MU	P-Az	None	MU, severe	2 y
3	M/52 MC/MU	P-Az	Metabolic disorder	MC, severe; MU, moderate	1 y
4	F/47 MC/MU	P-Az-MM-AMA-PL-MT-II	None	MC, moderate; MU, severe	2 y
5	M/34 MC/MU	P-Az-PL-II-AMA	Metabolic disorder	MC, severe; MU, severe	18 mo
6	M/38 MU	P-Az	Severe myopathy	MU, severe	8 mo
7	M/42 MC/MU	P-Az-AMA-PL	Diabetes mellitus	MC, severe; MU, severe	2.5 y
8	M/34 MC/MU	P-Az-CF	Femoral head fracture	MC, severe; MU, moderate	9 mo

Abbreviations: AMA, antiCD20 monoclonal antibody; Az, azathioprine; F, female; II, intravenous immunoglobulin; M, male; MC, mucocutaneous; MM, mycophenolate mofetil; MT, methotrexate; MU, mucosal; P, prednisone; PL, plasmapheresis.

^aAccording to scale described by Fleischli et al.¹¹ (For MC PV: no lesions; mild, fewer than 20 blisters; moderate, 20-40 blisters; severe, over 40 blisters. For MU PV: mild, 1-5 erosions; moderate, 5-10 erosions; severe, over 10 erosions or extensive erosions).

laboratory tests were performed regularly to test for potential adverse effects due to cyclophosphamide such as bone marrow suppression, immunosuppression, liver dysfunction, and hemorrhagic cystitis. All the patients were informed of the risks and benefits of cyclophosphamide therapy and informed consent was obtained in all cases. The patients were treated at the day hospital at our center. All of the patients were administered 10 to 15 mg/kg of intravenous cyclophosphamide diluted in 500 mL of saline solution for 90 minutes. The cycles were administered every 2 weeks. Patients were adequately hydrated with 500 mL of saline solution 2 hours before each session. Ondansetron (2 doses of 8 mg administered at 8-hour intervals) and granisetron (1 mg administered every 12 hours for 3 days) were used as antiemetic agents. The first dose of ondansetron was administered 1 hour before the pulse. This treatment was complemented with omeprazole to prevent gastroduodenal effects. A cycle was suspended when a patient's neutrophil count was under 1500/ μ L before the session. The protocol specified 10 cycles per patient, although the final number varied according to each patient's clinical and immunologic response.

In addition to cyclophosphamide, patients received high doses of prednisone (0.9-1 mg/kg/d), azathioprine (1.5-2 mg/kg/d), or mycophenolate mofetil (2-3 g/day) (Table 1). Prednisone treatment was tapered by 5 to 15 mg/d every month depending on clinical response and circulating levels of anti-Dsg1 and anti-Dsg3 antibodies. The gradual tapering of immunosuppressants (azathioprine or mycophenolate mofetil) began once a daily dose of 10 mg of prednisone was reached. Patients also received

alendronate at a dose of 70 mg per week. Several patients developed adverse reactions due to the administration of systemic corticosteroids (Table 1).

Results

All 8 patients included in the study exhibited excellent clinical and immunologic response (according to the criteria published by Fleischli et al¹¹) following the administration of ten 2-weekly cycles of intravenous cyclophosphamide. Overall, the lesions healed in a mean period of 5.1 months (range, 3-7 months) (Table 2). Clinical response to cyclophosphamide was observed in either an initial phase, in which lesions resolved completely during cyclophosphamide therapy, or in a later phase, in which patients continued to improve despite completion of therapy and tapering of prednisone and immunosuppressant doses.

Initial Response

Five patients (patients 1, 2, 6, 7, and 8) (62.5%) had achieved complete response on completion of the 10 cycles of cyclophosphamide, with a mean healing time of 4.4 months (range, 3-5 months) (Table 2). Active lesions were thus observed in just 3 patients (patients 3, 4, and 5) on completion of therapy. Furthermore, in all of these patients, it was possible to reduce the prednisone dose by over 50% at that time (Table 2). It is noteworthy that a substantial

Table 2. Response^a to 2-Weekly Pulse Intravenous Cyclophosphamide (Cy) Therapy

Patients	No. of Cy Cycles	Starting Cy Dose Maximum Cy Dose Total Cy Dose, mg	Adverse Reactions	Adjuvant Therapy	Prednisone Dose Before First Cycle of Cy	Prednisone Dose After Last Cycle of Cy	Disease Activity ^b After Last Cycle of Cy	EIS ^c Dsg1 Dsg3 Before First Cycle of Cy	EIS ^c Dsg1 Dsg3 After Last Cycle of Cy
1	10	1200 1200 12 000	Nausea and neutropenia	P + Az (100 mg/d)	70 mg/d	15 mg/d	No lesions after seventh cycle	1:20 168 190	1:10 neg 90
2	10	1100 1100 10 100	Nausea	P + MM (3 g/d)	60 mg/d	10 mg/d	No lesions after tenth cycle	1:20 neg 75	1:10 neg neg
3	10	900 1500 14 100	None	P + MM (3 g/d)	100 mg/d	60 mg/d	Mild	1:20 180 120	1:20 160 60
4	10	1500 1500 15 000	Nausea	P + MM (3 g/d)	60 mg/d	20 mg/d	Mild	1:80 99 160	1:20 neg neg
5	10	1800 1800 18 000	Nausea	P + MM (3 g/d) + 3 PL	60 mg/d	20 mg/d	Mild	1:1.280 182 253	1:80 135 226
6	10	1000 1000 10 000	Nausea	P + MM (3 g/d)	60 mg/d	20 mg/d	No lesions after sixth cycle	1:20 neg 45	neg neg neg
7	10	1800 1800 18 000	None	P + MM (3 g/d) + 3 PL	90 mg/d	50 mg/d	No lesions after tenth cycle	1:320 178 248	1:10 89 190
8	10	1700 1700 17 000	None	P + MM (3 g/d)	40 mg/d	15 mg/d	No lesions after tenth cycle	1:10 229 151	1:40 178 29

Abbreviations: Az, azathioprine; Dsg, desmoglein; EIS, epidermal intracellular substance; MM, mycophenolate mofetil; neg, negative; P, prednisone; PL, plasmapheresis.

^aResponse was excellent in all patients based on criteria described by Fleischli et al.¹¹ (Excellent indicates severe or moderate disease improving to absence of disease, none; good, severe disease improving to moderate or mild disease; minimal, moderate disease improving to mild disease; and none, no change or worsening of disease).

^bAccording to scale described by Fleischli et al.¹¹ (For MC PV: no lesions; mild, fewer than 20 blisters; moderate, 20-40 blisters; severe, over 40 blisters. For MU PV: mild, 1-5 erosions; moderate, 5-10 erosions; severe, over 10 erosions or extensive erosions).

^cDetermined by indirect immunofluorescence..

decrease was detected in antibody titers against Dsg1, Dsg3, and EIS in all patients. In patient 6, we were unable to find evidence of a PV immune response and in patients 2 and 4, we detected no anti-Dsg1 or anti-Dsg3 antibodies, although we did find low circulating levels of anti-EIS antibodies (Table 2). None of the patients developed active PV lesions on the skin or mucous membranes during follow-up. Clinical response, therefore, can be considered excellent in all cases (Table 3).

Late Response

Patients 3, 4 and 5 achieved complete clinical response in a mean of 6.5 months from the start of pulse therapy and a mean of 1.5 months from the completion of therapy. It is interesting to note that each patient experienced progressive clinical improvement after completion of therapy and with the progressive tapering of prednisone (to a dose of 10 mg/d). Adjuvant immunosuppressive

Table 3. Prolonged Clinical Response to 2-Weekly Pulse Intravenous Cyclophosphamide (Cy) Therapy

Patients	Follow-up Duration After Last Cycle of Cy, mo	Current Prednisone Dose	Current Adjuvant Immunosuppressive Therapy	Current PV Severity	Levels of Antibodies Against EIS/Dsg1/Dsg3
1	5	10 mg/d	Az, 100 mg/d	No lesions	neg/neg/83
2	5	15 mg/d	MM, 3 g/d	No lesions	1:20/neg/neg
3	15	5 mg/d	MM, 2 g/d	No lesions	neg/29/neg
4	23	2.5 mg/d	MM, 1.5 g/d	No lesions	neg/neg/neg
5	25	2.5 mg/d	MM, 1.5 g/d	No lesions	1:10/neg/57
6	25	2.5 mg/d	MM, 1 g/d	No lesions	neg/neg/neg
7	22 m	30 mg/d	MM, 3 g/d	No lesions	1:20/45/203
8	1	15 mg/d	MM, 3 g/d	No lesions	1:40/178/29

Abbreviations: Az, azathioprine; Dsg, desmoglein; EIS, epidermal intracellular substance; MM, mycophenolate mofetil; neg, negative; PV, pemphigus vulgaris.

therapy was also gradually reduced (Table 2) and a decrease in circulating titers of antibodies detected (Table 2). Anti-EIS antibody titers were slightly positive in just 4 patients (patients 2, 5, 7, and 8). Three patients (patients 2, 4, and 6) tested negative for both anti-Dsg1 and anti-Dsg3 antibodies (ELISA) and another 3 patients (patients 1, 3, and 5) tested negative for 1 of these antibodies. The remaining 2 patients (patients 7 and 8) tested positive for both antibodies but neither of them had developed new lesions 1 or 22 months after therapy. A slight increase in anti-Dsg1 and anti-Dsg3 antibodies was detected recently in patient 5 but there have been no flares in disease activity. These patients will need to be monitored regularly to test for new increases in antibody titers associated with PV activity. Finally, it is noteworthy that we were able to

reduce the starting dose of immunosuppressants in 4 patients (patients 3, 4, 5, and 6) (Table 3).

The Figure shows the results of treatment in 1 of the patients.

Adverse Reactions

We observed no significant adverse reactions in any of the 8 patients during the 2-weekly cyclophosphamide cycles. Five patients experienced nausea despite antiemetic therapy but the symptoms disappeared within a few days of the infusion. One patient developed transient neutropenia (800/ μ L), which required treatment with colony-stimulating factor; the neutrophil count improved

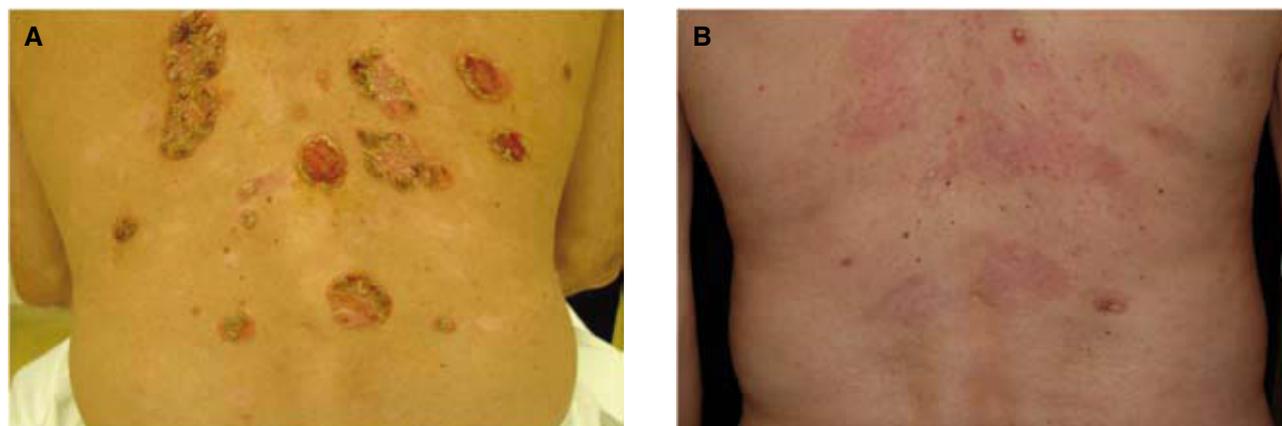


Figure. Clinical manifestations in patient 1. A, before cyclophosphamide cycles administered in association with corticosteroids and azathioprine. B, 1 month after last cycle of cyclophosphamide.

and remained within the normal range for the remaining cycles (Table 2). No other adverse reactions due to cyclophosphamide have been reported to date. We observed no adverse reactions associated with the administration of azathioprine or mycophenolate mofetil, or secondary infections due to immunosuppression.

Discussion

Systemic corticosteroid therapy is the most effective treatment in the initial phases of PV. The treatment is normally administered in combination with corticosteroid-sparing immunosuppressants such as azathioprine and mycophenolate mofetil.⁴ Cyclophosphamide, however, has also proven to be efficacious in PV but more adverse reactions have been reported when the drug is administered in low oral doses^{3,4,12-14} than when administered as intravenous pulse therapy,¹⁵⁻¹⁹ hence the establishment of diverse treatment regimens aimed at minimizing toxicity, reducing cumulative doses, and achieving better clinical response. Of note among the regimens described in the literature are the coadministration of cyclophosphamide and corticosteroids in monthly¹² or weekly²⁰ cycles, the monthly administration of cyclophosphamide in association with low doses of oral cyclophosphamide,^{8,11} the coadministration of cyclophosphamide and dexamethasone cycles,^{7,9,21} cyclophosphamide pulse therapy and plasmapheresis,^{22,23} concomitant cyclophosphamide and vincristine,²⁴ and immunoablative high-dose cyclophosphamide.^{25,26} Cyclophosphamide pulse therapy has also been administered in association with azathioprine and prednisone but only in isolated cases.¹¹

Clinical response was excellent in all 8 patients included in our study; with a 2-weekly regimen of intravenous cyclophosphamide, all the patients achieved complete clinical response (absence of active lesions) within a mean of 5.1 months. Five (62.5%) of the patients had no skin or mucous membrane lesions on completion of the 10 cycles, while the 3 remaining patients (37.5%) achieved complete clinical response after the tenth cycle, with a mean healing time of 6.5 months from the start of the regimen and 1.5 months from the last session. In 1 study that used pulse intravenous cyclophosphamide therapy at monthly intervals, clinical response was found to be excellent in 66% of patients and minimal in 22%.¹¹ In all the patients who responded clinically to treatment, disease control was achieved in 2 to 5 months. In another study that used the same treatment regimen, Bhat et al¹⁰ reported a mean healing time of 2.1 months for skin lesions and 3.6 months for mucosal lesions. The patients included in that study, however, had lesions on less than 10% of their body surface. Pasricha et al⁷ reported complete healing of PV lesions in

32% of patients treated with pulse dexamethasone and cyclophosphamide therapy in combination with low doses of oral cyclophosphamide. In those patients, it was possible to withdraw all treatment. Several years later, the same research group found that 72% of patients with PV achieved complete remission within a year of treatment with the above regimen (48.5% in 6 months and 23.5% in 12 months).²⁷

Current literature suggests administering intravenous cyclophosphamide as monthly pulses. This recommendation is based on the observation that a patient's leukocyte count begins to decrease gradually 2 to 3 days after initiation of treatment and reaches minimum levels after 10 to 12 days,^{8,28} which is when antibody production is most affected. The body begins to produce antibodies again within 1 to 2 weeks, which is when the repeated administration of cyclophosphamide might be most effective. Nonetheless, our initial experience showed us that patients experienced severe flares in disease activity 4 weeks after receiving intravenous cyclophosphamide and just before the next cycle. Considering this and reports of improved clinical response in patients with lymphomas treated with cyclophosphamide maintained at higher concentrations for longer, we decided to assess clinical response to the administration of 2-weekly rather than monthly cyclophosphamide in our patients. A similar regimen to ours, proposed by Pasricha et al,⁷ involved administering pulse cyclophosphamide therapy at 2-to-3-week intervals in patients with severe PV in order to induce earlier clinical remission and shorten the active disease phase. Intravenous cyclophosphamide therapy administered as 2-weekly pulses should therefore only be used in patients with highly active PV.

None of our patients have experienced flares in disease activity to date. Furthermore, titers of antibodies against and EIS, Dsg1, and Dsg3 showed a substantial progressive decrease both during and after pulse therapy. Even though patient 5 showed a slight increase in anti-Dsg1 and anti-Dsg3 antibody titers after 2 years of testing negative, he has not experienced any cutaneous or mucosal flare-ups to date. This patient will, however, require more frequent monitoring than the other patients due to an increased risk of relapse. Three patients (patients 1, 7, and 8) were still free of symptoms several months after completion of cyclophosphamide therapy, even though they had positive anti-Dsg1 and anti-Dsg3 titers. No flare-ups have been observed in any of the other patients either. Fleischli et al¹¹ reported flares in disease activity in almost 50% of patients administered pulse intravenous cyclophosphamide therapy at monthly intervals. In the study by Bhat et al,¹⁰ the corresponding percentage in a series of patients that received the same treatment was 34.6% 3 weeks to 8 months after completion of treatment. Pandya and Sontheimer⁸

reported similar results. Our findings therefore demonstrate that pulse intravenous cyclophosphamide, in association with corticosteroid-sparing immunosuppressants, can eliminate B-cell clones more efficiently when administered every 2 weeks than every month. While some patients may retain circulating levels of antibodies against Dsg1 and Dsg3, these antibodies appear to have a weak or possibly even inexistent role in the development of new PV lesions.

Adverse reactions to cyclophosphamide were negligible in our series, a finding which coincides with results reported for patients treated with monthly cycles of cyclophosphamide.^{7,10,11} Our patients will, nonetheless, need to be monitored regularly as we cannot rule out the possibility of future complications.

With our regimen, we were able to reduce the initial dose of prednisone by at least 50% in the majority of our patients and also to reduce the dose of immunosuppressants in a substantial proportion of patients. Only patient 7 is still receiving a moderate dose of prednisone. This 2-weekly regimen, therefore, also allows immunosuppressant doses to be reduced rapidly, considerably reducing the risk of adverse reactions while maintaining clinical efficacy.

Intravenous pulse cyclophosphamide therapy administered every 2 weeks could be indicated in patients with severe PV who do not respond to conventional immunosuppressive therapy, who develop adverse reactions due to medication (mostly corticosteroids), and who experience flares in disease activity despite high-dose corticosteroid therapy. More controlled studies, however, are required to evaluate the true role of cyclophosphamide in the management of PV and to assess the long-term safety of the drug. Furthermore, clear guidelines are needed to direct the approach and to make clear when we should use chemotherapy drugs such as intravenous cyclophosphamide or other drugs such as anti-CD20 monoclonal antibody²⁹⁻³¹ in association with other immunosuppressants in patients with severe PV.

Conflicts of Interest

The authors declare no conflicts of interest.

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