Pemphigus in Korea: A retrospective analysis of 199 patients over a 16-year period

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Pemphigus in Korea: A retrospective analysis of 199 patients over a 16-year period

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<ABSTRACT>

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Background: Pemphigus is a group of autoimmune blistering diseases of skin and mucous membrane with severe morbidity and occasional mortality. It is necessary to investigate the clinical features, treatment and long-term outcome of Korean patients with pemphigus as it is the most common and severe autoimmune bullous disease in Korea.

Objective: The aim of this study was to evaluate the clinical features, treatment outcomes and long-term prognoses of Korean patients with pemphigus.

Methods: We conducted a retrospective analysis of 199 patients diagnosed with pemphigus in Gangnam Severance Hospital between 1993 and 2008. Out of 199 total patients, 104 patients had pemphigus vulgaris (PV), and 95 patients had pemphigus foliaceus (PF). Treatment outcomes were calculated using Kaplan-Meier method and the pre-and post-rituximab severity scores were compared using a paired *t* test.

Results: We found that the mean age of onset was 46.1 ± 14.6 years, and the male to female ratio was equal. Systemic corticosteroids were the mainstay of treatment, and azathioprine was the most frequently used adjuvant therapy. We assessed treatment outcome according to a consensus statement

on the definition of the disease proposed by the International Pemphigus Committee. Overall remission (complete plus partial remission) was induced in 21%, 77% and 93% in PV patients 1,5 and 10 years after diagnosis, respectively, and in 51%, 87% in PF patients 1 and 5 years after diagnosis, respectively ($p < .001$, log rank test). Eight (7%) PV patients and five (5%) PF patients died during 16-year follow-up period. Sixteen patients (PV: 15, PF: 1) who were recalcitrant to conventional therapy received rituximab, and all of these patients achieved overall remission after 3-4 months from initiating treatment with rituximab. Mean pre- and post-rituximab pemphigus severity scores were 12.9 and 2.9 respectively ($p < .001$).

Conclusion: From this clinical study which followed up 199 Korean patients with pemphigus, most patients with pemphigus eventually could reach remission within 10 years of treatment. We confirmed that rituximab is a very effective and safe drug for severe pemphigus patients who are resistant to conventional therapy with early remissions being achieved.

Key words: pemphigus vulgaris, pemphigus foliaceus, Korean, clinical study, prognosis

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I. INTRODUCTION

Pemphigus is a chronic, severe blistering disease of the skin and mucous membrane caused by IgG autoantibodies to desmogleins of epidermal keratinocytes. Pemphigus is largely divided into pemphigus vulgaris (PV) and pemphigus foliaceus (PF) according to the site of intraepidermal blister formation, clinical features and targeting autoantigens. Before the advent of corticosteroids in the 1950's, PV was almost fatal.[1] Systemic corticosteroids, in combination with immunosuppressive agents have dramatically decreased a mortality rate of approximately 6%, but long-term corticosteroid use and immunosuppressive therapy still contribute to severe complication like infection.[1] In order to avoid these side effects, alternative treatments have been used. Recently, Intravenous gamma globulin (IVIG) and rituximab, an anti-CD 20 monoclonal antibody have shown improvement in severe recalcitrant cases of pemphigus.[2,3]

Because pemphigus is the most common autoimmune bullous disease in Korea and might have a high mortality rate if left untreated, researchers need to investigate the clinical features, treatment and long-term outcomes of pemphigus patients. However, previous clinical studies of pemphigus patients in Korea have provided limited data about the clinical features and long-term outcomes of pemphigus because the number of patients and follow-up duration were insufficient.[4,5]

A previous clinical study conducted by Herbst and Bystryn[6] revealed that 25%, 50%, and 75% of 40 PV patients eventually achieved complete and durable remission 2, 5, and 10 years after diagnosis during a 7.7-year follow-up period. However, it is obscure at present how many Korean patients with pemphigus can reach long-term remission.

Recently, the International Pemphigus Committee (IPC) proposed a consensus statement to accurately assess disease activity, severity and therapeutic response, because common terms and end point of pemphigus are needed for comparing disease severity and therapeutic outcomes between pemphigus treatment centers.

To our knowledge, this is the first clinical study for Korean pemphigus patients that enrolled a large number of patients and conducted long-term follow-up with the application of common terms from the IPC consensus statement to estimate treatment outcomes.

II. MATERIALS AND METHODS

1. Subjects

To evaluate the clinical features, treatment and prognoses of patients with pemphigus, the medical records of all patients with pemphigus diagnosed at Gangnam Severance Hospital in Seoul, Korea from 1993 to 2008 were reviewed retrospectively. The following data were recorded and analyzed; gender, age at onset, disease severity, treatment modalities, treatment outcome and time to remission.

Diagnosis was made on the basis of typical clinical features and confirmed by histopathology and immunofluorescence examinations.[7] Enzyme-linked immunosorbent assay (ELISA) for recombinant desmoglein (Dsg) 1 and Dsg3 were also performed in some of the patients. The patients who have more than 6 months follow-up data were included in this study to avoid a bias.

2. Statistical analysis

We compared demographic and clinical characteristics between PV and PF patients using independent two-sample *t* test for continuous variables and chi-square test for categorical variables. The cumulative probabilities of complete remission and overall remission (complete plus partial remission) were calculated using Kaplan-Meier method, and the curves were compared between PV and PF groups using the log rank test. We censored patients who did not achieve remission and those who were withdrawn during follow-up period. The pre-rituximab and post-rituximab pemphigus severity scores were compared using a paired *t* test. Two-sided $p < .05$ were considered significant. We used

SPSS for windows, version 17.0 (SPSS, Chicago, Illinois), for all statistical analyses.

3. Assessment methods

A. Disease severity score

Scores for disease severity were assessed using our revised criteria modified from those designed by Herbst and Bystryn[6], who minutely divided the body areas involved, plus an additional oral mucosa score. The following grading system was devised to provide objective scores for disease severity and treatment outcome (Table 1).

The disease extent was graded from 0 to 6+ based on the number of body areas involved. If the oral mucosa were severely involved, a score of 2+ was assigned, and if the mucosa were mildly involved, a score of 1+ was recorded. Therapy intensity was graded from 0-6+ based on the corticosteroid dose and type of adjuvant therapy required to control disease activity. A score from 0 to 3+ was given according to the dose of corticosteroids (expressed in milligrams per day of prednisolone). If an adjuvant therapy such as azathioprine, cyclosporine, mycophenolate mofetil, or dapsone was used, a score of 1+ was assigned. If an adjuvant therapy such as cyclophosphamide, prednisolone pulse, intravenous immunoglobulin, or rituximab was used, a score of 2+ was recorded (Table 1).

PV disease severity was graded on a 0-14+ scale, while PF disease severity was graded on a 0-12+ scale based on the sum of disease extent and intensity of therapy. PV disease severity was classified as

mild, moderate or severe based on a severity score of 0-4, 5-8 or 9-14, respectively, and PF disease severity was classified as mild, moderate or severe based on a severity score of 0-3, 4-7 or 8-12, respectively (Table 2). Scores were recorded at the initial visit and during all follow-up visits.

Table 1. Severity score was measured by extend of disease and intensity of therapy.

Extend of disease	**Score**	**Intensity of therapy**	**Score**
scalp, face/ neck, chest/ abdomen/ back/ arm/ leg	1 in each body area involved	Pd 10mg > 10~30mg > 30mg <	1 2 3
oral mucosa (only for PV)		Adjuvant therapy	
mild	1	AZA, MMF, CsA, Dapsone	1
severe	2	CTX, Pd pulse, IVIG, Rituximab	2

Pd: prednisolone, AZA: azathioprine, MMF: mycophenolate mofetil, CsA: cyclosporine A, CTX: cyclophosphamide, Pd pulse: prednisolone pulse, IVIG: intravenous immunoglobulins

Table 2. The disease severity was classified by severity score.

Severity	**PV severity score (total 14)**	**PF severity score (total 12)**
Mild	0~4	0~3
Moderate	5~8	4~7
Severe	9~14	8~12

B. Late end points of disease activity

Concerning treatment outcome, we used the consensus of statement on definitions of disease activity and therapeutic response proposed by the International Pemphigus Committee in 2008 (Table 3).[8]

Table 3. Definition of late observation point proposed by the International Pemphigus Committee

Complete remission off therapy	Absence of new or established lesions while the patient is off all systemic therapy for at least 2 months
Complete remission on therapy	The absence of new or established lesions while the patient is receiving minimal therapy
Partial remission off therapy	Presence of transient new lesions that heal within 1 week without treatment and while the patient is off all systemic therapy for at least 2 months
Partial remission on minimal therapy	The presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy, including topical steroids
Relapse/flare	Appearance of $\geq$3 new lesions/month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved disease control

4. Treatment protocol

According to pemphigus severity scores, the patients were divided into mild, moderate and severe group. We treated patients with the following treatment protocol (Fig 1). If the disease severity was mild, we initially treated the patients with systemic corticosteroid alone. But, for moderate cases and mild cases who did not show improvement, we added immunosuppressive agents including azathioprine,

mycophenolate mofetil, dapsone, cyclosporine or cyclophosphamide to control the disease. For patients who did not tolerate the above immunosuppressive drugs, we administered intravenous immunoglobulin (IVIG) (IV drip infusion at 400 mg/kg/d administered in divided dose over 5 consecutive days). For patients with severe disease activity, we initially treated the patients with prednisolone pulse therapy (intravenous, pulse administration of prednisolone, 500-750mg/d for 3 days) or IVIG therapy. If the disease activity of severe cases was controlled, combined therapy with systemic corticosteroid and immunosuppressants was maintained to achieve remission. Rituximab was administered for the patients who had poor response to the above conventional therapies (intravenous rituximab 375 mg/m^2 , 2 or 3 weekly infusion).

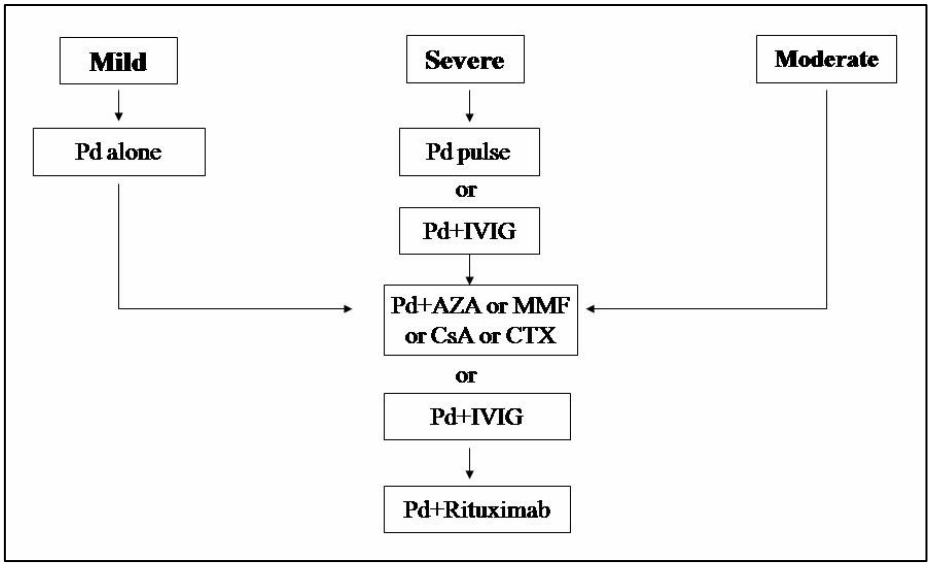

Figure 1. Treatment protocol for pemphigus. Mild patients were treated with prednisolone (Pd) alone. For therapy resistant cases, immunosuppressive drugs (eg, azathioprine, mycophenolate mofetil, dapsone, cyclosporine or cyclophosphamide) were added to control the disease. In case of moderate disease activity, prednisolone in combination with immunosuppressants were used initially to control the disease. For patients with severe disease activity, we initially treated the patients with prednisolone pulse therapy. If controlled, combined therapy with systemic corticosteroid and immunosuppressants was maintained to achieve remission. For patients with systemic disease like diabetes, hepatitis, renal failure, intravenous immunoglobulin (IVIG) was administered to avoid side-effects. Rituximab was administered for the patients who had poor response to the above conventional therapies. (Pd: prednisolone, AZA: azathioprine, MMF: mycophenolate mofetil, CsA: cyclosporine A, CTX: cyclophosphamide, Pd pulse: prednisolone pulse, IVIG: intravenous immunoglobulins)

III. RESULTS

1. Clinical characteristics of pemphigus patients

Out of 199 pemphigus patients, 104 patients were diagnosed with PV and 95 patients were diagnosed with PF. Therefore the prevalence rate of PV to PF is 1.1:1.0. For the 104 PV patients, the mean age of onset was 47.0 years (range, 19-75 years), the male-to-female ratio was 1.0:1.0 (men 51, women 53), and the mean follow-up duration was 48.6 months (range, 6-172 months). For the 95 PF patients, the mean age of onset was 45.0 years (range, 24-83 years), the male-to-female ratio was 1.0:1.1 (men 46, women 49), and the mean follow-up duration was 45.9 months (range, 6-181 months). We didn't observe any significant differences between PV and PF patients in terms of gender and age. The clinical characteristics for our patients with PV and PF are summarized in Table 4.

With regard to the disease severity at initial visit, eighty-six patients with PV (83%) had moderate to severe disease, whereas 82 PF patients (86%) had mild to moderate disease (figure 2).

Table 4. Summary of clinical characteristics of 199 pemphigus patients

	PV	**PF**	***P* value**
Number of patients	104	95	
Mean age at onset (years)	47.0±13.7	45.0±15.5	0.408
Sex ratio (M:F)	51:53(1:1.04)	46:49(1:1.07)	0.931
Follow up duration (months)	48.6±36.9	45.9±39.6	0.587
Skin involvement*	99(95.2%)	95(100%)	0.061
Oral mucosa involvement*	102(98.1%)	0(0%)	.

Results are presented as number (%) or mean ± SD (standard deviation).

*****at initial visit

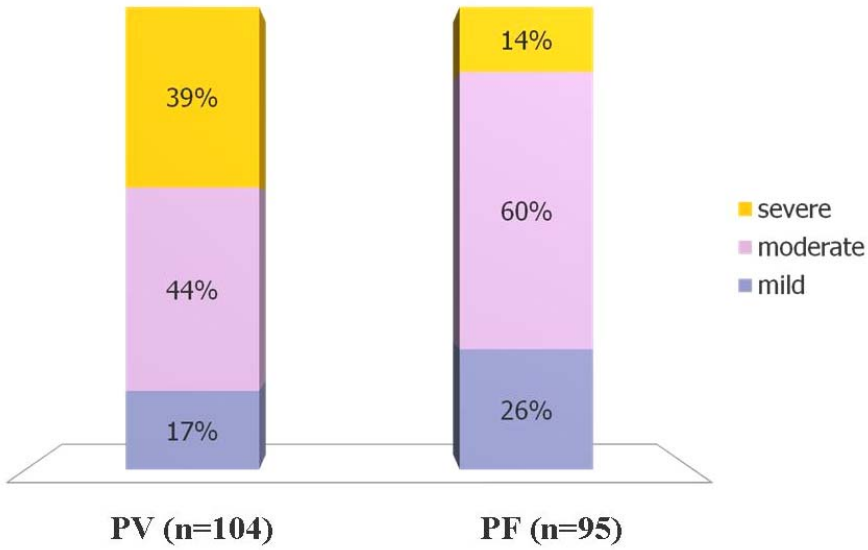

Figure 2. Disease severity at initial visit. Of the 104 PV patients, 39%, 44% and 17% of PV patients had severe, moderate and mild disease severity, respectively. Of the 95 PF patients, 14%, 60% and 26% of PF patients had severe, moderate and mild disease severity, respectively. Almost PV patients (83%) had moderate to severe disease at the initial visit, whereas the majority of PF patients (86%) had mild to moderate disease at initial visit.

2. Treatment regimens

As a therapeutic agent, systemic corticosteroid was the mainstay of treatment, and the average initial dose of oral prednisolone was 25.4 ± 15.3 mg in PV patients and 17.6 ± 10.6 mg in PF patients (*p* for difference = .037, independent two-sample *t* test). Twelve (11.5%)

patients with PV and 41 (43.2%) PF patients received prednisolone alone (p < .001). Ninety-two (88%) patients with PV and 54 (57%) PF patients received adjuvant therapies (p < .001). Azathioprine was the most frequently used drug as adjuvant therapy for both PV and PF patients. Fifteen (14%) patients with PV and one (1%) patient with PF who were recalcitrant to conventional therapy received 4-6 time infusions of rituximab (Table 5).

Table 5. Treatment summary of 199 pemphigus patients

	PV (n=104)	**PF (n=95)**	***P* value**
Initial prednisolone dose (mg/day)	25.4±15.3	17.6±10.6	0.037
Prednisolone alone	12(11.5%)	41(43.2%)	<0.001
Prednisolone +Adjuvant	92(88.5%)	54(56.8%)	<0.001
Azathioprine	48(52.2%)	32(59.3%)	0.406
Cyclophosphamide	25(27.2%)	12(22.2%)	0.507
Mycophenolate mofetil	28(30.4%)	7(13%)	0.017
Cyclosporine	15(16.3%)	5(9.3%)	0.232
Dapsone	2(2.2%)	11(20.4%)	<0.001
Prednisolone pulsed IV	36(35%)	14(15%)	0.01
Intravenous immunoglobulins	9(9%)	1(1%)	0.020
Rituximab	15(14%)	1(1%)	<0.001

Results are presented as number (%) or mean $\pm$ SD (standard deviation).

3. Treatment outcome

A. Both PF complete and overall remission rate were higher in PF patients than PV patients.

Complete remission was induced in 10.8%, 32.8%, 47.4%, 61.8%, and 72.7% of PV patients and in 28.4%, 48.2%, 69.1%, 83.5%, and 83.5% of PF patients 1, 3, 5, 7, and 10 years after diagnosis, respectively (Fig 3). PF patients achieved more complete remission compared to PV patients ($p = .002$).

Overall remission (complete plus partial remission) was induced in 21%, 55.9%, 71.2%, 89.7%, and 93.5% of PV patients and in 50.9%, 75.1%, 87.2%, 95.7%, and 97.9% of PF patients 1, 3, 5, 7, and 10 years following diagnosis, respectively. PF patients achieved more overall remission compared to PV patients ($p < .001$).

PF patients achieved remission earlier than PV patients ($p = .002$). Of the PV patients, 22%, 15%, 4%, and 42% reached complete remission off therapy, complete remission on therapy, partial remission off therapy, and partial remission on therapy, and 27%, 9%, 4%, and 33% of PF patients reached complete remission off therapy, complete remission on therapy, partial remission off therapy, and partial remission on therapy, respectively. The percentage of PV patients reached remissions were higher than those of PF patients except complete remission off therapy (Table 6).

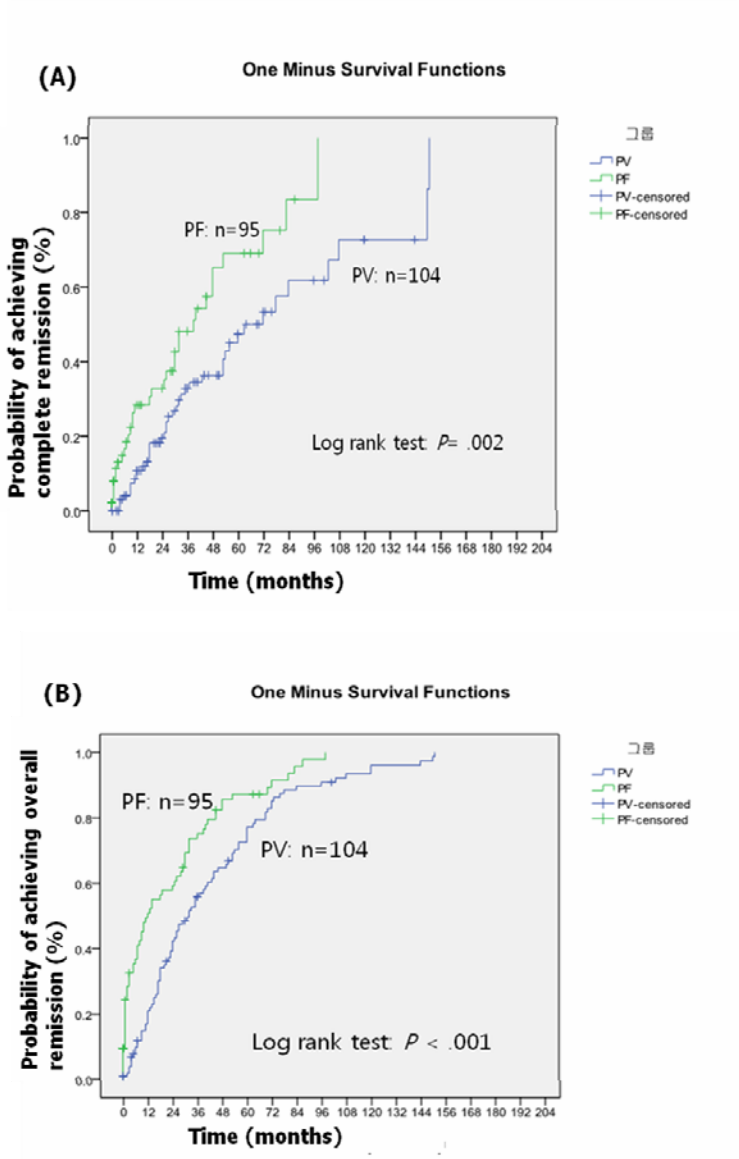

Figure 3. Cumulative (A) complete remission and (B) overall remission rates for PV and PF patients who achieved remission during follow-up time. The survival curves are statistically significant between PV and PF patients ((A) $p = .002$, (B) $p < .001$).

Table 6. Summary of outcome of 199 pemphigus patients

	PV (n=104)		PF (n=95)	
	Number of patients	**Time to remission (months)**	**Number of patients**	**Time to remission (months)**
Overall remission	93	36.5±34.9	67	17.1±23.9
Complete remission off	22(21.2%)	56.1±42.1	25(26.3%)	26.3±24.3
Complete remission on	19(18.3%)	21.3±15.7	9(9.5%)	18.8±27.6
Partial remission off	5(4.8%)	39.4±24.8	4(4.2%)	39.8±45.3
Partial remission on	47(45.2%)	38.9±33.6	32(33.7%)	16.5±18.4
No remission	3(2.9%)		23(24.2%)	
Mortality	8(7.7%)		5(5.3%)	

Results are presented as number (%) or mean ± SD (standard deviation).

B. Prednisolone (Pd) plus adjuvant immunosuppressive therapy compared with Pd alone in patients with pemphigus

There was no significant difference in time to remission between Pd alone groups and Pd plus adjuvant treatment group, but in PF patients, Pd alone group achieved overall remission earlier than Pd plus adjuvant treatment group ($p < .001$).

Table 7. Comparison of outcomes of prednisolone with adjuvant therapy and without in patients with PV and PF.

	Median time to CR(months)			Median time to OR(months)		
	Pd alone	**Pd plus Adjuvant**	**P value**	**Pd alone**	**Pd plus Adjuvant**	**P value**
PV	60	72	0.752	25	45	0.105
PF	17	35	0.712	3	30	< .001

CR: complete remission, OR: overall remission, Pd: prednisolone

C. Conventional therapy plus rituximab compared with conventional therapy alone in patients with pemphigus

All patients who received rituximab experienced remarkable clinical improvements. The average pemphigus severity score decreased from 12.9 to 2.9 after rituximab treatment ($p < .001$)(Figure 5). Out of the 16 patients, one patient reached complete remission off therapy 10 months after treatment of rituximab (Figure 6), 8 patients reached complete remission on therapy 6 months after treatment, and 7 patients reached partial remission on therapy 15 months after treatment. The mean time to disease control (time interval between baseline and control) was 2-3 weeks, and the mean time to remission was 3.8 months. In contrast, the severe PV group without rituximab therapy (29 patients) achieved remission after an average of 52 months of conventional therapy. PV group with rituximab therapy achieved complete remission ($p = .001$) and overall remission ($p = .045$) earlier than PV group without rituximab therapy (Table 8). We could not estimate remission rate during the follow-up period, because only one PF patient received rituximab

therapy.

Out of the 16 patients who received rituximab, 5 patients relapsed after a mean follow up period of 18.8 months, and these patients reached remission again after two more infusions of rituximab. The time to remission after the second rituximab infusion was 2 months. No significant adverse effects were observed except one patient who developed transient pruritic rash that occurred 30 minutes after infusion.

Table 8. Comparison of outcomes of conventional therapy and conventional therapy with rituximab in patients with PV

	Median time to CR (months)			**Median time to OR(months)**		
	Conventional therapy	**Conventional therapy plus rituximab**	**P value**	**Conventional therapy**	**Conventional therapy plus rituximab**	**P value**
PV	72	17	0.001	33	17	0.045

CR: complete remission, OR: overall remission, Pd: prednisolone

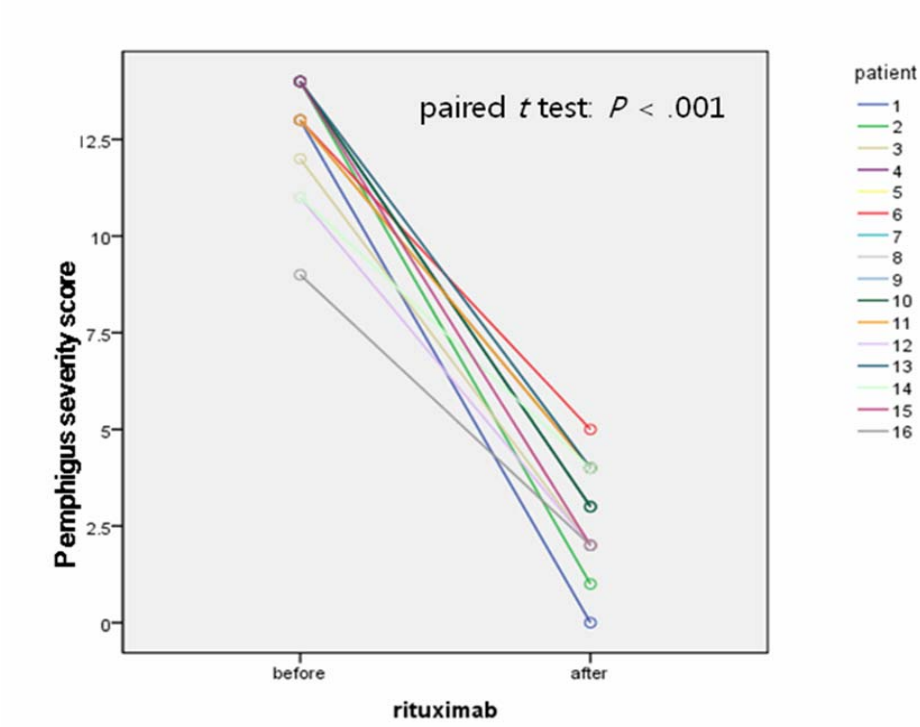

Figure 5. Comparison of pemphigus severity score before and after rituximab treatment. Sixteen patients with pemphigus who were recalcitrant to conventional therapy received 4-6 time infusions of rituximab. The average pemphigus severity score decreased from 12.9 to 2.9 after rituximab treatment（$p < .001$). The mean time to remission was 3.8 months, and the follow-up duration after treatment was 36 months.

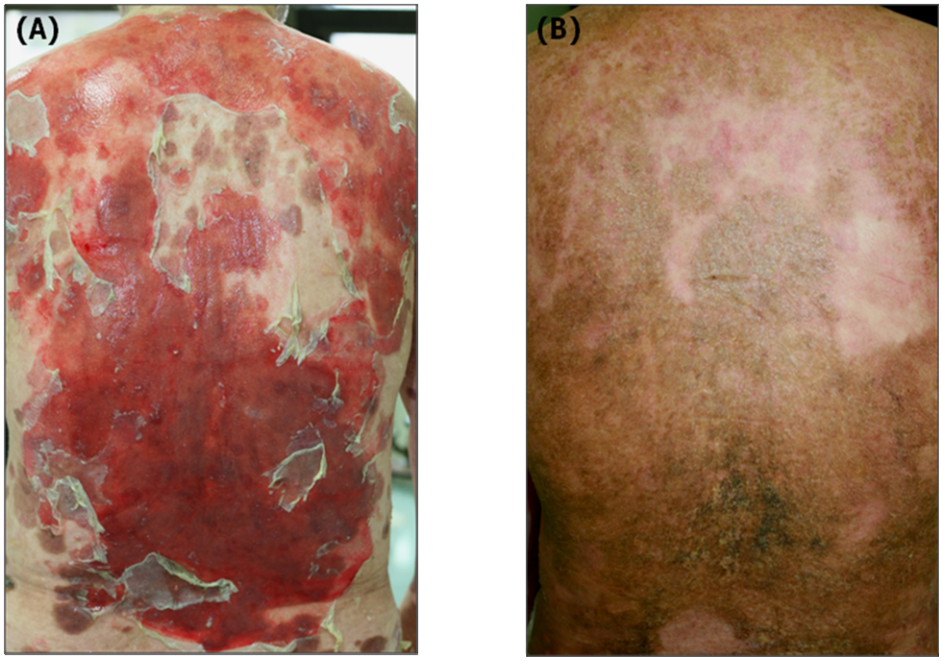

Figure 6. Clinical response to rituximab in recalcitrant pemphigus vulgaris (PV). (A) A representative patient with severe PV involving the whole body before rituximab treatment.
(B) Clinical presentation after finishing the fifth infusion of rituximab treatment (after 3 months). Eight weeks after the first infusion, the lesions started to heal and after 10 months complete remission off therapy was achieved.

D. Mortality

During the 16-year follow-up period, eight (7%) PV patients and five (5%) PF patients died (Table 6). Out of the PV deaths, sepsis was the cause of death in three cases, and hepatic failure, lung cancer, esophageal cancer, gastric perforation, and suicide was the cause of death in each patient. Out of the PF deaths, four patients died due to sepsis and one patient died due to cardiorespiratory failure.

IV. DISCUSSION

Pemphigus is a rare autoimmune blistering disorder varying in incidence from 0.5 to 3.2 cases per 100,000 people per year.[9] Lee[10] reported that pemphigus is the most common immunobullous disease in Korea, varying in incidence from 0.1-0.5 cases per 100,000 people per year. We also confirmed that pemphigus is the most common immunobullous disease in Korea and bullous pemphigoid is the second common disease (unpublished data).

The incidence of pemphigus subtype is dependent on the ethnic background. In New York, Los Angeles, and Croatia where the Jewish, Middle Eastern, and Mediterranean population predominates, the ratio of PV to PF cases is approximately 5:1 whereas in Finland, it is only 0.5:1.0.[11] Previous Korean studies revealed that PV was the predominant clinical subtype, however, this study demonstrated that the prevalence of PV and PF is almost same.[4,5] A previous study from Korea revealed a female-to-male ratio was 1.3:1, and Japanese study revealed female-to-male ratio was 2:1. [5,12] A study from Israel including 155 patients revealed the female-to-male ratio was 1.5:1.[13] However, in our study the female-to-male ratio was approximately 1:1 for both PV and PF. This result is similar to the previous studies from Malaysia and Finland.[14,15]

Pemphigus primarily affects middle-aged patients, and in our study the mean age of onset was 46.0 years (PV, 47.0 years; PF, 45.0 years). However, eight PV patients (7.7%) and 15 PF patients (15.8%) first developed pemphigus lesions in their later teens or twenties. Therefore if young patients present with blisters on their skin or in their oral cavity, physicians should consider pemphigus as a differential diagnosis and appropriately evaluate further.

Similar to other studies, we found that prednisolone and immunosuppressive agents were the mainstays of therapy for our patients.[2] We determined the treatment regimen based on pemphigus subtype, disease severity and other associated diseases. In general, mild cases were treated with systemic corticosteroid alone, and moderate and severe cases were treated with a combination therapy of systemic corticosteroids and immunosuppressants including azathioprine, mycophenolate mofetil, cyclosporine and cyclophosphamide. The average initial dose of oral prednisolone in PV patients was higher than that for PF patients ($p = .037$), and more PV patients received adjuvant therapies than PF patients ($p = < .001$). This is closely related to the fact that most PV patients had moderate to severe disease, while most PF patients had mild to moderate disease at the initial visit.

We used relatively small initial dose of prednisolone (0.3-0.5mg/kg/day) to control the disease, while other institutes usually treated patients with high initial dose of prednisolone (1mg/kg/day). This is because we favored low dose of systemic corticosteroid in order to avoid long-term side effects. In addition, patients were not likely to take high dose of corticosteroid, because many of them had negative perception of systemic corticosteroid.

We found that in PV patients, there were no difference in remission between prednisolone alone group and prednisolone with adjuvant therapy group, but in PF patients, prednisolone alone group had more favorable prognosis than prednisolone with adjuvant therapy group. This is because PF group composed much more mild patients than PV. Therefore, we consider that disease severity is a more important prognostic factor than adjuvant therapy.

Although systemic corticosteroids, in combination with immunosuppressive agents have improved prognosis of pemphigus remarkably, treatment of pemphigus is still challenging. Long-term use of

immunosuppressive therapy also increase the chance of adverse effect or complications. Furthermore some patients are unresponsive to conventional immunosuppressive treatments, so novel effective therapy is required. Rituximab is a chimeric monoclonal antibody that binds to the CD20 antigen on the surface of B cells and has been proved to be effective in recalcitrant pemphigus.[3,16] Joly[16] et al. reported that 18 of 21 (86%) patients with severe PV or PF had complete remissions three months after a single cycle of four weekly infusions of rituximab. In the case reported by Cianchini[17] et al, 10 PV patients and 2 PF patients achieved prolonged clinical remission after a single course of rituximab treatment. In this study, all 16 patients who received rituximab showed successful controlling of the disease, producing complete remission in 9 patients and partial remission in 7 patients during 16 month follow-up period. Also, PV group with rituximab therapy achieved both complete remission and overall remission significantly earlier than PV group without rituximab therapy. We confirmed that rituximab is an effective and safe treatment option for patients unresponsive to conventional therapies.

With regard to the treatment outcomes and prognoses, overall remission (complete plus partial remission) was induced in 21%, 53%, 71%, 87%, and 89% of PV patients 1, 3, 5, 10, and 15 years after diagnosis, respectively. Herbst and Bystryn[6] reported that complete and long-lasting remission (no evidence of disease and no systemic therapy for at least six months) was induced in 25%, 50%, and 75% of 40 PV patients 2, 5, and 10 years after diagnosis, respectively. In this study, we achieved more remission rate than previous study.[6] This difference is partially because our definition of remission is more generous than those of previous studies and we could introduce more effective therapy like rituximab in some patients. This study confirmed that PF patients achieved higher rates of complete and overall remission than PV patients[11] ($P = .002$, $P < .001$, respectively).

The overall mortality rate in pemphigus has been reported to be 5-9%[18], and the most common cause of death is attributed to the side effects of treatment.[1,19,20] In our study, the overall pemphigus mortality rate was around 7% during the 16-year follow-up period and the most common cause of death is sepsis which was comparable with the results of a previous study. One of our patients who is a 49-year-old female with severe PV committed suicide during treatment. As pemphigus is difficult to control and is a relapsing disorder which destroys the patient's appearance and requires long-term period of treatment, the disease creates significant psychological problems for patients and may lead to depression and even suicide.[21] Therefore, we propose that doctors should carefully evaluate pemphigus patients' psychological distress and treat the patients appropriately.

V. CONCLUSION

The aim of this study is to evaluate the clinical features, treatment outcomes and long-term prognoses of Korean patients with pemphigus. The summary of the results are described below.

1. The mean age of onset was 46.1 ± 14.6 years, and the male to female ratio was equal.
2. Most patients with pemphigus reached complete plus partial remission during follow-up period.
3. Rituximab is an effective and safe drug for severe pemphigus patients who are resistant to conventional therapy with early remissions being achieved.

In conclusion, this study is the first large scale follow-up study for pemphigus patients of Korea. We conducted long-term follow-up observation with the application of common terms from the International Pemphigus Committee consensus statement to estimate treatment outcomes. This study should enhance our understanding of clinical characteristics and long-term prognosis in pemphigus patients.

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< ABSTRACT(IN KOREAN)>

한국인 천포창:
16년 동안 199명의 환자를 대상으로 한
후향적 연구

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배 경: 천포창(pemphigus)은 피부와 점막에 수포를 형성하는 만성 수포성 질환으로서 심할 경우 사망까지 할 수 있는 심각한 질환이다. 한국에서 천포창은 자가면역수포성 질환 가장 빈도가 높으며, 치료하지 않을 경우 사망률이 높은 위중한 피부병이기 때문에 치료와 예후에 대한 분석이 매우 중요하다.

목 적: 본 연구의 목적은 한국인 천포창 환자의 임상적 특징, 치료 결과, 장기 예후 등을 분석하여 규명하는데 있다.

방 법: 본 연구자들은 지난 16년간 강남세브란스병원 피부과 수포성질환 클리닉에서 진단 및 치료 한 199명의 천포창 환자의 임상적 특징과 치료 효과 및 예후를 분석하고자 차트 리뷰를 통한 후향적 연구를 시행하였다.

결 과: 한국인 천포창 환자를 대상으로 한 이번 연구에서는 심상성 천포창 (pemphigus vulgaris)과 낙엽상 천포창

(pemphigus foliaceus)이 같은 비율로 발생하였으며, 심상성 천포창과 낙엽상 천포창 모두에서 남성과 여성이 같은 발생비율을 보였다. 평균적으로 중년에 질병이 발생하였으며, 평균 초발연령은 46세였다. 치료로는 전신적 스테로이드를 기본적으로 사용하였으며, 면역억제제 중에서는 azathioprine이 가장 많이 사용되었다. 본 연구에서는 2008년 국제 천포창 연합 (International Pemphigus Committee)에서 제시한 천포창의 관해에 관한 정의에 관한 합의내용을 적용하여, 한국인 천포창 환자의 치료후 결과에 대해 분석 하였다. 유병기간에 따라 관해의 비율을 분석해 본 결과 심상성 천포창 환자는 1년, 5년, 10년 후에 각각 21%, 71%, 87%의 환자가 부분관해 이상에 도달하였으며, 낙엽상 천포창 환자는 각각 41%, 68%, 74%의 환자가 부분관해 이상에 도달하였다. 16년간의 연구 기간 동안 총 8명의 심상성 천포창 환자와 5명의 낙엽상 천포창 환자가 사망하였다. 기존 치료법에 잘 반응하지 않는 난치성 천포창 환자 16명 (심상성 천포창: 15명, 낙엽상 천포창: 1명)에게 rituximab을 투여하였고, 모든 환자가 평균적으로 rituximab 치료시작 3~4개월 후에 완전관해나 부분관해에 도달하였다.

결 론: 199명의 한국인 천포창 환자를 대상으로 한 본 연구에서 심상성 천포창과 낙엽상 천포창의 발병률의 차이는 없었으며, 성별에 따른 유병률도 동일하였다. 질병은 주로 중년에 시작하였으며, 사망률은 7%로, 이는 과거의 외국 및 국내 보고와 큰 차이가 없었다. 거의 대부분의 천포창

환자는 유병기간이 10년이 지나면 결국에는 관해에 도달하였다. 또한 본 연구에서는 rituximab이 기존 치료에는 효과가 없는 난치성 천포창 환자에게 사용할 수 있는 안전하고 효과적이며 빨리 관해에 도달하게 하는 유용한 약제라는 것을 확인하였다.

핵심되는 말: 심상성 천포창, 낙엽상 천포창, 한국인, 임상적 연구, 예후