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CLINICAL REPORT

Epidermolysis Bullosa Acquisita: A Retrospective Clinical Analysis of 30 Cases

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Epidermolysis bullosa acquisita (EBA) is an acquired, autoimmune blistering disorder caused by autoantibody production against type VII collagen. The aim of this study was to examine the clinical types, treatments, and outcomes of 30 patients with EBA. In our cohort, the median age of onset was 44.0 years, with a similar incidence for both genders (46.7% male, 53.3% female). The majority of patients had classic type (36.7%) and bullous pemphigoid (BP)-like type (46.7%) EBA. The remaining patients had mucous membrane pemphigoid-like (6.7%), Brunsting-Perry pemphigoid-like (6.7%), and linear IgA bullous dermatosis-like type (3.3%) EBA. All patients were treated initially with a combination of methylprednisolone, dapsone and colchicine. No significant differences in time to remission were identified between patients with classic vs. BP-like EBA. In a second subset analysis of 19 patients, a group treated with high-dose (>8 mg) methylprednisolone achieved remission earlier (median time to remission: 3 months) than a group treated with low-dose (≤8 mg) methylprednisolone (median time to remission: 12 months), irrespective of clinical type ($p=0.003$). ***Key words: epidermolysis bullosa acquisita; retrospective study, clinical study remission.***

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Epidermolysis bullosa acquisita (EBA) is a blistering disease associated with autoantibody production against type VII collagen, the major component of the anchoring fibrils that connect the basement membrane zone to the papillary dermis (1, 2). Although the exact pathophysiologic process in EBA remains unclear, circulating autoantibodies against type VII collagen in patients with EBA ultimately result in subepidermal blister formation with concomitant inflammation, milia and scarring (3).

The mucocutaneous lesions of EBA can be quite varied and mimic other types of autoimmune bullous disease. Currently, 5 clinical presentations of EBA have been identified: (*i*) classic (4); (*ii*) bullous pemphigoid (BP)-like (5); (*iii*) mucous membrane pemphigoid (MMP)-like (6); (*iv*) Brunsting-Perry pemphigoid-like (7); and (*v*) linear lgA bullous dermatosis (LAD)-like type (Table I) (8). The classic form of EBA is a non-inflammatory mechanobullous disease primarily involving trauma-prone areas of skin, such as the hands, elbows, knees, and feet, and in some cases the oral mucosa. BP-like EBA is an inflammatory vesiculobullous eruption that mainly involves the trunk, central body, extremities, skin folds and, in some cases, the oral mucosa. Individuals with disease that primarily affects mucosal surfaces are defined as having the MMP-like EBA, while Brunsting-Perry pemphigoid-like EBA is a chronic, recurrent blistering disease confined to the head and neck. LAD-like type presents with linear IgA deposits in the basement membrane zone that can be observed with direct immunofluorescence (9).

EBA is a chronic disease that is often refractory to many treatment modalities. Generally, patients with EBA require supportive care, such as wound management and education regarding trauma prevention, especially in individuals with the classic mechanobullous type of the disease. However, while some patients with EBA respond well to treatment with dapsone (10), colchicines (11) and cyclosporine, many patients, particularly those with

Table I. *Clinical types of epidermolysis bullosa acquisita (EBA)*

Clinical type	
Classic EBA	A non-inflammatory mechanobullous disease primarily involving trauma-prone areas of skin, such as the hands, elbows, knees, and feet, and in some cases the oral mucosa
Bullous pemphigoid-like type EBA	An inflammatory vesiculobullous eruption that mainly involves the trunk, central body, extremities, skin folds, and in some cases the oral mucosa
Mucous membrane pemphigoid-like type EBA	A disease that primarily affects mucosal surfaces
Brunsting-Perry pemphigoid-like type EBA	A chronic, recurrent blistering disease confined to the head and neck
Linear IgA dermatosis-like type EBA	A disease that presents with linear IgA deposits in the basement membrane zone that can be observed with direct immunofluorescence

classic mechanobullous disease, respond poorly to systemic corticosteroids and immunosuppressive agents (e.g. azathioprine, methotrexate and cyclophosphamide) (9). More recently, both extracorporeal photochemotherapy (12) and intravenous immunoglobulin (13) have also been reported to be effective in some patients with EBA.

To date, only a few clinical studies of EBA have been conducted, presumably because EBA is a relatively rare disease (14). No significant etiologic factors for EBA have been identified in the previous clinical studies, although one study did report an association between the HLA-DR2 allele and EBA (15). Most estimates indicate the prevalence of EBA to be 1 case per 1.3 million people in Germany and 4 cases per 3.6 million people in France (16, 17). Here, we conducted a retrospective clinical analysis of 30 patients with EBA to determine the clinical manifestations of the disease and evaluate treatment outcomes. Statistical analyses were employed to evaluate any differences in treatment outcome between classic and BP-like type EBA and to identify any correlations between systemic corticosteroid dose and therapeutic efficacy.

MATERIALS AND METHODS

All data for this study were collected retrospectively from the medical records of 30 patients diagnosed with EBA over a 16-year period (1994–2009) in the Department of Dermatology of Gangnam Severance Hospital, Seoul, Korea. In all individuals, diagnosis was made by clinical and histologic features, and later confirmed through immunofluorescence and immunoblot analyses (Table II). In the present study, we evaluate age of onset, clinical type, duration of follow-up, medical treatments, comorbidities, and time to remission.

Here, we used the definitions of remission for EBA by modification of definition of remission for pemphigus suggested by the International Pemphigus Committee (18). "Complete remission (CR) off therapy" was defined as the absence of new and/or established lesions for at least two months without treatment. "Complete remission on therapy" was defined as the absence of new lesions while the patient is receiving minimal therapy. "Minimal therapy" was defined as less than or equal to 8 mg/day of methylprednisolone with or without adjuvant therapy including dapsone and colchicines for at least two months. "Partial remission (PR) off therapy" was defined as the presence of transient new lesions that heal within one week without treatment for at least two months. "Partial remission on minimal therapy" was defined as the presence of transient new lesions that heal within one week while the patient is receiving minimal therapy.

The treatment protocol for patients with EBA is described below. Initially, all patients were treated with combination therapy of low-dose methylprednisolone, dapsone and colchicine. Patients with mild clinical features (less than 10% of body involvement) initially were prescribed ≤ 8 mg/day of methylprednisolone, while patients with severe clinical features (more than 10% of body involvement) were prescribed >8 mg/day of methylprednisolone. Systemic corticosteroid dosage was later adjusted by therapeutic response. For dapsone, patients were initially prescribed a dose of 25 mg/day, which

Table II. *Patient characteristics*

Patient No.	Sex/age (years)[a]	Clinical type	DIF	Salt-split DIF	Salt-split IIF	IIF	Western blot
1	F/78	1	IgG, IgA, C3	Dermal	Dermal	1:40	ND
2	F/24	1	IgG, IgA, C3	Dermal	Negative	0	ND
3	F/37	1	IgG, IgA	Dermal	Negative	0	ND
4	F/66	1	IgG, C3	Dermal	Dermal	1:20	Positive
5	F/68	1	IgG, C3	Dermal	Dermal	1:160	ND
6	F/41	1	Negative	ND	Dermal	1:40	Positive
7	M/59	1	Negative	ND	Dermal	1:160	Positive
8	F/83	1	C3	Dermal	Dermal	1:5	Positive
9	M/73	1	IgG	Dermal	Dermal	1:10	Positive
10	M/60	1	IgG	Dermal	Negative	0	Positive
11	M/45	1	IgG, IgA	Dermal	Negative	0	ND
12	F/74	2	IgG, IgA, C3	Dermal	Negative	0	ND
13	F/45	2	IgG, IgA, IgM, C3	Dermal	Negative	0	Positive
14	F/55	2	IgG, IgA	Dermal	Negative	0	ND
15	F/35	2	IgG, C3	Dermal	Dermal	1:20	ND
16	M/72	2	IgG, C3	Dermal	Dermal	1:640	Positive
17	M/39	2	IgG, IgA, C3	Dermal	Dermal	1:160	Positive
18	M/52	2	IgG, C3	Dermal	Dermal	1:40	ND
19	M/31	2	IgG, IgA, C3	Dermal	Dermal	1:16	Positive
20	F/47	2	IgG, C3	Dermal	Negative	0	Negative
21	F/39	2	IgG, IgA, C3	Dermal	Negative	0	ND
22	F/67	2	IgG, C3	Dermal	Dermal	1:640	Positive
23	M/35	2	IgG, C3	Dermal	Dermal	1:80	ND
24	M/70	2	IgG, IgA, C3	Dermal	Negative	0	ND
25	M/55	2	IgG, C3	Dermal	Dermal	1:20	Positive
26	F/66	3	Negative	ND	Dermal	1:320	Positive
27	M/66	3	IgG, C3	Dermal	Negative	0	Negative
28	M/55	4	IgG, C3	Demral	Negative	0	Negative
29	F/27	4	IgG, C3	Dermal	Dermal	1:160	ND
30	M/29	5	IgA	Dermal	Negative	0	ND

[a]Age at time of writing. Clinical type: 1=classic type; 2=bullous pemphigoid-like type; 3=mucous membrane pemphigoid-like type; 4=Brunsting-Perry pemphigoid-like type; 5=linear IgA dermatosis-like type; ND: not done; DIF: direct immunofluoroscence; IIF: indirect immunofluoroscence.

was gradually increased up to 100 mg/day as tolerated. For colchicine, patients were maintained on a dose of 1.2 mg/day. Other immunosuppressive medications, such as cyclophosphamide, mycophenolate mofetil, cyclosporine and azathioprine, were considered if patients did not respond to the combination therapy of methylprednisolone, dapsone and colchicine.

To assess the relationship between systemic corticosteroid dose and therapeutic efficacy, we stratified the patients into two groups: a high-dose steroid (HDS) group that received > 8 mg/day of methylprednisolone for at least one month; and a low-dose steroid (LDS) group that received ≤ 8 mg/day of methylprednisolone for at least one month. We performed a subset analysis of 19 patients with EBA treated with methylprednisolone, dapsone and colchicine by a single physician. Patients who were prescribed other immunosuppressive agents, including systemic corticosteroid pulse therapy, cyclophosphamide, mycophenolate mofetil, cyclosporine or azathioprine, were excluded from this subgroup.

Baseline characteristics were summarized by EBA type using descriptive statistics. All descriptive summaries are presented with a median and range for continuous variables and a count and percentage for categorical variables. Fisher's exact test and Wilcoxon rank-sum test were performed to compare the clinical features between two groups (classic vs. BP-like type and HDS vs. LDS group). Comparison of time to remission was done by log-rank test. All analyses were performed with SAS (version 9.1, SAS institute, North Carolina, USA) using an alpha level of 0.05.

RESULTS

In our cohort, the median age at disease onset was 44.0 (range 21–79) years, with 14 (46.7%) male patients and 16 (53.3%) female patients. The median length of follow-up period was 23.0 (range 0.3–155) months. Classification by clinical phenotype revealed 11 (36.7%) individuals with classic, 14 (46.7%) with BP-like, 2 (6.7%) with MMP-like, 2 (6.7%) with Brunsting-Perry pemphigoid-like, and 1 (3.3%) with LAD-like type. The clinical features of the varying EBA patient types are shown in Table III. No significant differences were identified between patients with classic and BP-like types in terms of sex (male 36.4% vs. 50%, $p = 0.6887$), age of onset (median age 58.0 years vs. 43.0 years, $p = 0.2721$), duration of follow-up (median duration 25.0 vs. 23.0 months, $p = 0.7571$), maximum methylprednisolone dose over a one-month period (median dose 8.0 vs. 16.0 mg, $p = 0.5149$) and oral involvement (7 of 11 patients vs. 6 of 14 patients).

All patients were initially treated with combination therapy of methylprednisolone, dapsone and colchicine. Other immunosuppressive therapies, including cyclophosphamide, mycophenolate mofetil, cyclosporine or azathioprine, were prescribed for 6 (20%) patients who did not respond to the initial regimen (Table IV). Treatment was well tolerated in most patients, with the exception of one 37-year-old patient who developed a cataract after 10 years of corticosteroid therapy. After analyzing our database, the following diseases were considered as co-morbid disease associated with EBA: 3 patients with diabetes mellitus, two patients with systemic lupus erythematosus. Another patient died approximately one year after diagnosis as a result of an esophageal stricture secondary to mucosal involvement.

The median time to remission for the 30 patients with EBA was 9 months. From a cross-sectional point of view, complete remission was observed in 33.3% of individuals (8/24), and partial remission in 20.8% (5/24) at one year after treatment initiation. Complete remission was achieved in 33.3% (5/15) of patients at 3 years after diagnosis, and 45.5% (5/11) at 6 years after diagnosis. Partial remission was seen in 33.3% of individuals (5/15) at 3 years after diagnosis and 45.5% (5/11) at 6 years after diagnosis (Fig. 1). We also compared median time to remission between patients with classic EBA ($n = 11$) and BP-like EBA ($n = 14$). The median time to remission was 10 months in classic patients with EBA and 18 months in BP-like patients with EBA (Table II). No statistical differences were identified between two types in time to remission ($p = 0.3367$) and complete remission ($p = 0.9431$) (Fig. 2).

According to the treatment dosage of methylprednisolone, patients were stratified into the HDS group (6 patients), and the LDS group (13 patients). The resulting Kaplan–Meier curves demonstrate that significantly better responses to treatment were achieved in the HDS group irrespective of clinical types. The median time to remission was 3 months in the HDS group and 12 months in LDS group ($p = 0.003$) (Fig. 3).

Table III. *Clinical features of epidermolysis bullosa acquisita (EBA) patients. No statistical differences were observed in age, sex, maximal dose of corticosteroid or oral involvement between classic and bullous pemphigoid (BP)-like EBA*

	Clinical type					
	Classic	BP-like	MMP-like	Brunsting-Perry pemphigoid-like	LAD-like	Total
Number of patients (M/F)	11 (4/7)	14 (7/7)	2 (1/1)	2 (1/1)	1 (1/0)	30 (14/16)
Median age of onset, years (range)	58.0 (21–79)	43.0 (28–67)	56.5 (49–64)	24.5 (24–25)	28.0	44.0 (21–79)
Median follow-up duration, months (range)	25.0 (1–96)	23.0 (0.3–155)	86.5 (21–152)	20.5 (13–28)	10.0	23.0 (0.3–155)
Maximum dose of MPD at least 1 month, mg (range)	8.0 (0–48)	16.0 (4–72)	8.0	2.0 (0–4)	16.0	8.0 (0–72)
Oral involvement, *n* (%)	7 (63.6)	6 (42.9)	2 (100)	0	0	15 (50)
Time to remission[a], months, *n*	10	18				

[a]Complete remission plus partial remission.

MMP: mucous membrane pemphigoid; LAD: linear IgA bullous dermatosis; MPD: methylprednisolone.

Table IV. *Six patients who were treated with other immunosuppressive drugs*

Pat. No.	Sex/age (years)	Clinical types	Immunosuppressive drugs	Duration of treatment before the beginning of other immunosuppressive drugs	Remission time
1	F/78	Classic	Methylprednisolone pulse therapy (methylprednisolone 500 mg for 3 days)	1 month	3 months
3	F/37	Classic	Mycophenolate mofetil 2000 mg Methylprednisolone pulse therapy (methylprednisolone 500 mg for 3 days)	1 month	10 months
13	F/45	BP-like	Mycophenolate mofetil 1500 mg Pulse therapy with methylprednisolone and cyclophosphamide (methylprednisolone 500 mg for 3 days and cyclophosphamide 500 mg for 1 day)	36 months	72 months
17	M/39	BP-like	Cyclosporine 100 mg	30 months	63 months
25	M/55	BP-like	Azathioprine 100 mg	1 month	No remission
26	F/66	MMP-like	Pulse therapy with methylprednisolone and cyclophosphamide (methylprednisolone 500 mg for 3 days and cyclophosphamide 500 mg for 1 day)	1 month	23 months

BP: bullous pemphigoid; MMP: mucous membrane pemphigoid.

DISCUSSION

Our results show that the classic and BP-like presentations are the two most common clinical types of this disease. In our cohort, generalized inflammatory BP-like EBA was slightly more common than the classic form, which primarily affects trauma-prone extensor skin surfaces. No comparisons between the other subtypes, including MMP-like, Brunsting-Perry pemphigoid-like, and LAD-like EBA, could be made due to the small number of patients in our cohort. We did not find the classic type to be statistically different from the BP-like type in terms of age of onset, sex, maximum prescribed dose of systemic corticosteroids and oral involvement.

In our clinic, we used a combination of a low-dose systemic steroids, dapsone, and colchicine as a first-line therapy. Colchicine is often used as a first-line drug because of its low incidence of serious side-effects (11), and, in this study, all patients were prescribed colchicine at a dose of 1.2 mg/day. Dapsone is another safe and effective medication used in the treatment of EBA (10). In this study, all patients with EBA were initially prescribed dapsone at a dose of 25 mg/day, which was gradually increased up to 100 mg/day as tolerated. Although some previous reports recommend the use of high-dose systemic corticosteroids in EBA (19, 20), we use relatively low doses (8 mg for the classic type and 16 mg for BP-like type as median maximum methylprednisolone doses) to avoid the side-effects often associated with long-term corticosteroid use. Notably, we were able to achieve favorable outcomes (9 months of time to remission) without serious side-effects with this regimen.

Although some data has linked EBA with inflammatory bowel disease (IBD) (21–23), none of the patients in our cohort had EBA with comorbid IBD. The incidence and prevalence of IBD in Korea are lower than that in North America and Europe, although they are increasing. In addition, IBD patients in Korea are associated with different genomics from those in Western countries (24). These reasons may explain the low incidence of IBD among our patients with EBA. Also, EBA has been reported to be associated with systemic diseases, including rheumatoid arthritis, diabetes mellitus, cryoglobulinaemia, psoriasis and systemic lupus erythematosus (9, 25). There were three patients with diabetes mellitus and two with systemic lupus erythematosus in our study. The most severe complication

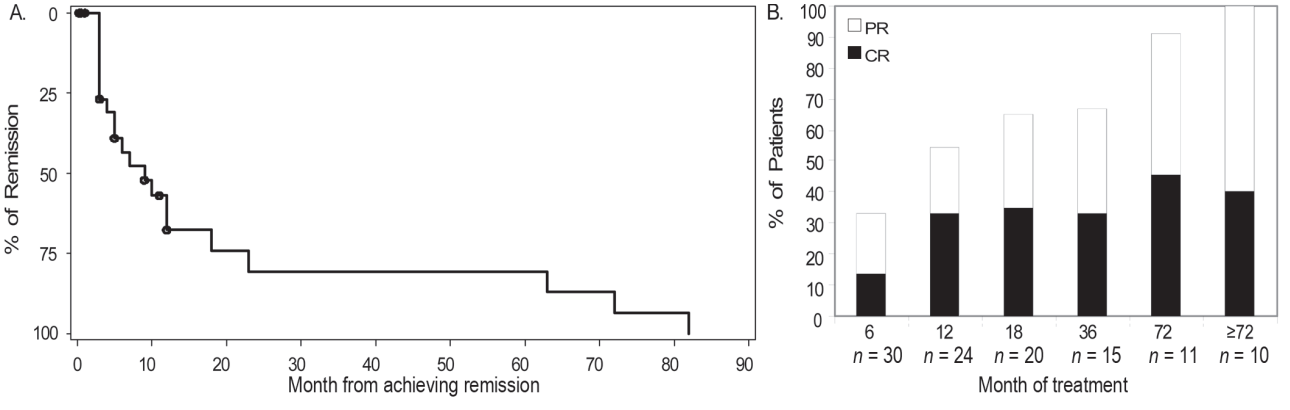

Fig. 1. Time to remission for 30 patients with epidermolysis bullosa acquisita (EBA). (A) Kaplan–Meier curve of remission in EBA. Median time to remission was 9 months. (B) Cumulative remission rate of patients with EBA by treatment duration. One year after therapy initiation, partial remission (PR) was achieved in 20.8% (5/24 patients) and complete remission (CR) in 33.3% (8/24 patients).

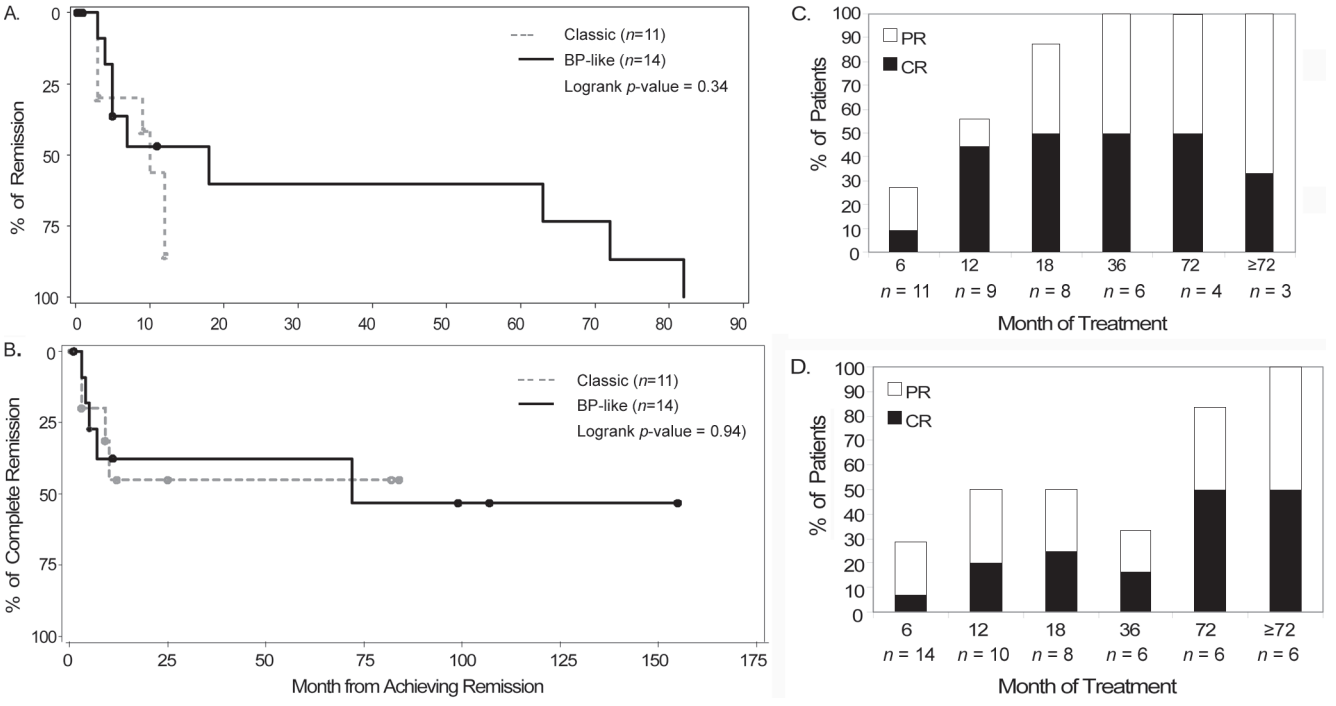

Fig. 2. Comparison of time to remission between classic and bullous pemphigoid (BP)-like epidermolysis bullosa acquisita (EBA) ($n=25$). (A) Kaplan–Meier curve of remission (partial remission (PR) plus complete remission (CR)) in two different types: classic and BP-like type. No statistical differences were identified in the time to remission between classic ($n=11$) and BP-like ($n=14$) EBA (10 months vs. 18 months, $p=0.3367$). (B) Kaplan–Meier curve of CR showed that there were no statistical differences in the time to CR between classic and BP-like EBA ($p=0.94$). (C), (D) Cumulative remission rate of classic and BP-like type by treatment duration. Rates of PR and CR between classic and BP-like type were assessed after the first year of treatment (PR; 11.1% vs. 30% CR; 44.4% vs. 20%) and the third year of treatment (PR; 50% vs. 50% CR; 50% vs. 33.3%). Time to CR was not different between classic and BP-like types ($p=0.9431$).

that developed in our patients with EBA was esophageal stricture, which correlated with severe mucosal involvement (26). Other minor common problems were secondary skin infections, milia, scarring and fibrosis.

We also compared the demographics and clinical course of classic EBA with BP-like EBA. The classic presentation appears to convey a more favorable outcome, with faster median times to remission than the BP-like presentation. However, we did not find any statistical differences between the two types.

In our comparison of the groups treated with low- and high-dose systemic corticosteroids, we were unable to identify any differences in baseline demographics, including sex ratio, clinical types and median age of onset (Table V). However, the HDS group did show significantly shorter times to remission compared with the LDS group, irrespective of clinical type. Moreover, while the clinical disease activity of the HDS group was more severe at baseline, relatively better outcomes were nevertheless achieved in this group. These data suggest that higher doses of systemic corticosteroids (specifically > 8 mg/day of methylprednisolone) not only treat

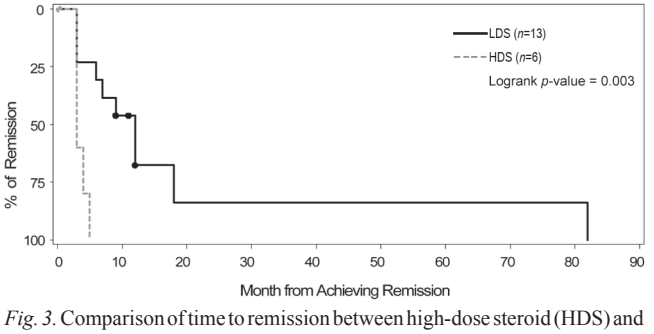

Fig. 3. Comparison of time to remission between high-dose steroid (HDS) and low-dose steroid (LDS) group ($n=19$). A HDS group ($n=6$) demonstrated better outcomes than a comparable LDS group ($n=13$) (3 months vs. 12 months, $p=0.003$). High dose: > 8 mg of methylprednisolone for at least one month; low dose: ≤ 8 mg of methylprednisolone for at least one month.

Table V. *Demographics by high-dose steroid (HDS) and low-dose steroid (LDS) group. No statistical differences were observed in sex, clinical types, or age of onset between the HDS and LDS group (*p *= 1.0000, 0.7147 and 0.6807 for each variable)*

	LDS group	HDS group	*p*-value
Male to female ratio	6:7	2:4	1.0000
Clinical type, *n* (%)			
Classic	5 (71.4)	2 (28.6)	0.7147
BP-like	5 (62.5)	3 (37.5)	
MMP-like	1 (100)	0 (0)	
Brunsting-Perry pemphigoid-like	2 (100)	0 (0)	
LAD-like	0 (0)	1 (100)	
Age at onset, years, median (min, max)	44.0 (21.0, 79.0)	37.5 (28.0, 61.0)	0.6807
Time to remission, months	12	3	0.0030

BP: bullous pemphigoid; MMP: mucous membrane pemphigoid; LAD: linear IgA bullous dermatosis.

patients with EBA more effectively, but also expedite the time to remission.

In conclusion, the median time to remission for EBA was 9 months in our cohort. No significant differences were identified between classic-type and BP-like type EBA in terms of age of onset, sex, treatment intensity, median time to remission and oral involvement. A group of patients treated with higher doses of corticosteroids (>8 mg/day of methylprednisolone for at least one month) showed more favorable outcomes than individuals treated with lower doses of corticosteroids (≤8 mg/day of methylprednisolone for at least one month).

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