Received: 31 May 2020 | Revised: 8 June 2020 | Accepted: 8 June 2020

DOI: 10.1002/cia2.12126

ORIGINAL ARTICLE

Journal of Cutaneous Immunology and Allergy

WILEY

Doxycycline as an initial treatment of bullous pemphigoid in Japanese patients

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Abstract

Objectives: Tetracycline antibiotics have been used in bullous pemphigoid (BP) for their anti-inflammatory effects. In Japan, tetracycline and minocycline, but not doxycycline, have been generally used in BP, although doxycycline has a better side-effect profile than other tetracycline antibiotics. To determine the effectiveness and safety of doxycycline in Japanese BP patients, we performed a retrospective cohort study.

Methods: We analyzed 27 Japanese BP patients in whom doxycycline was used as a first-line treatment at Kido Hospital between April 1, 2014, and August 31, 2019. We estimated time to prednisolone treatment as a primary measure of effectiveness of doxycycline, because second-line prednisolone treatment was initiated when each physician judged that disease activity could not be controlled with doxycycline alone.

Results: During the median follow-up of 63 weeks, second-line prednisolone treatment was initiated in 22 of 27 patients. Median time to prednisolone treatment was 7 weeks. Severe disease based on the Bullous Pemphigoid Disease Area Index (BPDAI) and eosinophilia were the risk factors for prednisolone treatment. At 6 weeks, 14 of 27 patients were under doxycycline treatment without prednisolone, and significant decreases of BPDAI scores were achieved. In 9 of these 14 patients, prednisolone treatment was started after 6 weeks, but the recurrent or mild remaining lesions could be controlled with relatively low-dose prednisolone in combination with doxycycline. No severe adverse events related to doxycycline occurred.

Conclusions: Doxycycline has short-term effectiveness, potential corticosteroid-sparing effect, and long-term safety in Japanese BP patients with mild to moderate disease and no eosinophilia.

KEYWORDS

bullous pemphigoid, doxycycline, Japan, safety, treatment outcome

1 | INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune subepidermal bullous disease that mainly affects the elderly and is associated with IgG autoantibodies against 180-kDa BP antigen (BP180)/type XVII collagen and/or 230-kDa BP antigen (BP230).[1] Systemic corticosteroid is the standard treatment of BP, but might cause severe adverse events especially in elderly patients. In randomized controlled trials of BP patients, whole-body application of superpotent topical corticosteroid, clobetasol propionate (10-30 g/day), was shown to be as effective as oral prednisone with fewer adverse events.[2,3] However, this treatment is not practical for patients who cannot apply the topical agent to the whole body every day.

Tetracycline antibiotics have been used as a treatment of BP[4-9] for their anti-inflammatory effects.[10-12] The Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial, a multi-center prospective randomized controlled trial conducted in Europe, showed that oral doxycycline (200 mg/day) is not inferior to oral prednisolone (PSL) (0.5 mg/kg/day) in short-term disease control and is significantly safer than PSL as an initial treatment of BP.[13] In the Japanese guidelines for the management of pemphigoid,[1] tetracycline or minocycline with or without nicotinamide, but not doxycycline, is recommended as a first-line treatment of mild BP, mainly because doxycycline has not been widely used in Japan. However, tetracycline and minocycline are known to be associated with adverse events such as gastrointestinal symptoms, dizziness, pigmentation, and interstitial pneumonia, more frequently than doxycycline.

At our hospital, we have used doxycycline as an initial treatment in most BP patients since April 1, 2014. To determine the effectiveness and safety of doxycycline in Japanese BP patients, we performed a retrospective cohort study of BP patients treated initially with doxycycline at our hospital.

2 | METHODS

2.1 | Patients

Between April 1, 2014, and August 31, 2019, 33 patients with newly diagnosed BP were treated at Kido Hospital. The diagnosis of BP was made based on the subepidermal blistering and presence of anti-BP180 and/or anti-BP230 autoantibodies. From the 33 patients, 4 patients in whom systemic corticosteroids had already been given by the practitioners without diagnosis before referring to our hospital were excluded. Two patients in whom PSL was used as an initial treatment at our hospital were also excluded. One of these patients had mild disease based on the Bullous Pemphigoid Disease Area Index (BPDAI),[1,14] but a locum tenens physician initiated PSL treatment (0.4 mg/kg/day) on diagnosis. In another patient with moderate disease, PSL (0.6 mg/kg/day) was used as an initial treatment, because of the history of drug allergy to uncertain antibiotics. A cohort of the remaining 27 patients treated initially with doxycycline was analyzed in this study.

2.2 | Treatment

Oral doxycycline (200 mg/day) was started at the date of diagnosis in all 27 patients. Lesional but not whole-body application of topical corticosteroids was used in combination with doxycycline. Clobetasol propionate was used in most patients except for a patient with mild disease in whom difluprednate was used, and the dose was ≤10 g/day in most patients except for a patient with severe disease (20 g/day). When each physician judged that disease activity could not be controlled with the first-line doxycycline treatment, second-line treatment with oral PSL was started. In refractory patients, immunosuppressant or high-dose intravenous immunoglobulin was added.

2.3 | Data collection

We reviewed the medical charts and collected the following data at the time of diagnosis: patient age, sex, associated diseases, BPDAI, disease severity based on BPDAI, eosinophil counts, and serum levels of IgG autoantibodies against the noncollagenous 16a (NC16a) domain of BP180 determined by the chemiluminescent enzyme immunoassay. Clinical course and outcome of each patient including the number of blisters and BPDAI at 6 weeks after doxycycline treatment were also recorded.

2.4 | Statistical analysis

Time to PSL treatment was calculated from the date of start of doxycycline until the date of start of PSL. Patients who were not treated with PSL until the last contact or beyond the end of the follow-up period at October 31, 2019, were censored at the date of the last contact before October 31, 2019. Time to PSL treatment according to the candidate risk factors was estimated using the Kaplan-Meier method, and curves were statistically compared using the log-rank test. Possible independent roles of the different factors that were significant in the univariate analyses at the $P = .1$ level were estimated in multivariate analyses using the Cox proportional hazards regression model with a backward elimination of variables that were not significant at the $P = .05$ level. BPDAI scores before and after the treatment were compared using paired t test. All reported P-values are two-tailed with a value less than .05 considered significant. Statistical calculations were performed using JMP software (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

Characteristics of the 27 patients are summarized in Table 1. Patient age ranged from 66 to 93 years, and the female to male ratio was

TABLE 1 Characteristics of the patients

Characteristics	n	Mean (SD)
Age (years)		82.4 (7.3)
Sex		
Female	17	
Male	10	
Neurological disorders		
–	2	
+	25	
Malignancy		
–	24	
+	3	
Diabetes mellitus		
–	19	
+	8	
BPDAI		
Skin: erosions/blisters		9.5 (7.8)
Skin: urticaria/erythema		13.2 (22.1)
Mucosa: erosions/blisters		0 (0)
Disease severity		
Mild	15	
Moderate	10	
Severe	2	
Eosinophil count (/μL)		828.5 (750.1)
Normal (<500)	12	
High (≥500)	15	
Anti-BP180 NC16a IgG (U/mL)		232.8 (499.4)
<9.0	2	
≥9.0	25	

1.7:1. All patients were Japanese. Twenty-five patients had neurological disorders, and 3 patients had malignancy. Eight patients had diabetes mellitus, and 4 patients had been taking a dipeptidyl peptidase 4 inhibitor (DPP-4i) before disease onset. As increased risk of BP during DPP-4i intake was reported,[15] DPP-4i was discontinued in all 4 patients, but none showed improvement of BP. Japanese patients with DPP-4i-associated BP tend to show a noninflammatory phenotype with few erythematous lesions and have anti-BP180 autoantibodies against epitopes outside the NC16a domain.[16-18] All 4 patients exhibited a typical inflammatory phenotype. Three patients had serum anti-BP180 NC16a IgG at diagnosis, and in 1 patient who had anti-BP180 autoantibodies against the non-NC16a region at diagnosis, anti-BP180 NC16a IgG became positive during the follow-up period.

Based on BPDAI, most patients had mild (15 patients) to moderate (10 patients) disease, while two patients had severe disease. None had mucosal lesions. Peripheral blood eosinophilia (≥500/μL) was observed in 15 patients. Anti-BP180 NC16a IgG was detected in the sera of all patients except for a patient with DPP-4i-associated BP and another with anti-BP230-type BP.[19]

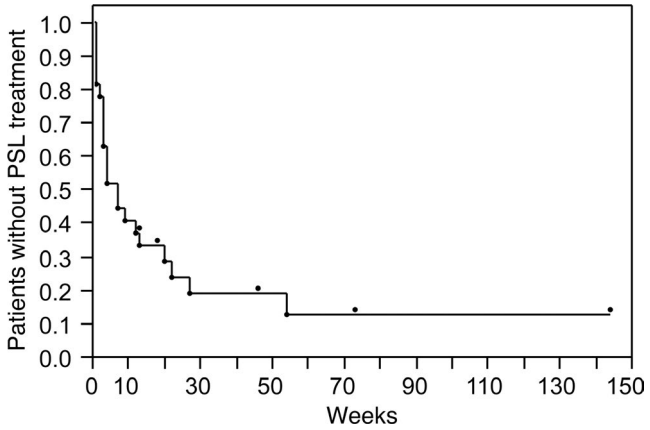

FIGURE 1 Kaplan-Meier curve for time to PSL treatment

3.2 | Effectiveness

As this was a retrospective study and PSL was used as the second-line treatment for all patients in whom disease activity could not be controlled with doxycycline alone at the discretion of each physician, we estimated time to PSL treatment as a primary measure of effectiveness of doxycycline. During the median follow-up of 63 weeks (range, 8-144 weeks), PSL treatment was initiated in 22 of 27 patients. Kaplan-Meier curve for time to PSL treatment is shown in Figure 1. Median time to PSL treatment was 7 weeks (range, 1-144+ weeks). PSL was started at 0.3 mg/kg/day in 11 patients and 0.4-0.6 mg/kg/day in 11 patients. Doxycycline was discontinued in 2 patients at the start of PSL treatment. Severe disease and eosinophilia were identified as the risk factors for PSL treatment in the multivariate analysis (Table 2), but age, sex, associated diseases, or anti-BP180 NC16a IgG level was not significantly associated with risk for PSL treatment.

The primary efficacy outcome of the BLISTER trial was treatment success (≤3 blisters) at 6 weeks, and in the doxycycline arm, treatment success was achieved in 74% at 6 weeks by both modified intention-to-treat and per-protocol analyses.[13] In our cohort, 14 of 27

TABLE 2 Risk factors for PSL treatment

Factors	Hazard ratio	95% confidence interval	*P*-value
Disease severity			
Mild	1.00	–	–
Moderate	1.82	0.73-4.57	.197
Severe	8.25	1.08-45.27	.044
Eosinophil count			
Normal	1.00	–	–
High	3.02	1.12-9.08	.028

patients (9 with mild disease and 5 with moderate disease at diagnosis) were under doxycycline treatment without PSL at 6 weeks. Treatment success (≤3 blisters) was achieved in 13 of these 14 patients (93%) and in 25 of all the 27 patients (93%) at 6 weeks. The 14 patients without PSL treatment at 6 weeks showed significant decreases of BPDAI scores of both erosions/blisters and urticaria/erythema (Figure 2). Nevertheless, PSL treatment was eventually started in 9 of these 14 patients at 7-54 weeks (median 13 weeks), because of the recurrence after complete clearance of BP lesions or incomplete disease control (a small number of new blisters and/or urticaria/erythema) during doxycycline treatment. The recurrent or mild remaining lesions were treated successfully with relatively low-dose (0.3 and 0.4 mg/kg/day in seven and two patients, respectively) PSL in combination with doxycycline.

Although some patients were censored during PSL tapering, 26 of 27 patients had no active BP lesions (no erosions/blisters or urticaria/erythema) at the last contact under no treatment (three patients), doxycycline alone (2), doxycycline and ≤0.2 mg/kg/day PSL (3), doxycycline and >0.2-0.4 mg/kg/day PSL (3), ≤0.2 mg/kg/day PSL alone (9), and >0.2-0.4 mg/kg/day PSL with or without immunosuppressants (6). One patient was transferred to a long-stay hospital during early phase of the treatment because of decrepitude.

3.3 | Safety

Adverse events possibly related to doxycycline were observed in three of 27 patients (Table 3). All adverse events were reversible, and no severe (grade ≥3) adverse events occurred.

4 | DISCUSSION

In this single-center retrospective cohort study, we evaluated the effectiveness and safety of doxycycline in Japanese BP patients. We have shown that median time to PSL treatment, the primary outcome of effectiveness employed in this study, was 7 weeks, and the risk factors for PSL treatment were severe disease and eosinophilia. During the follow-up period, no severe adverse events related to doxycycline occurred. Although we cannot directly compare our results with the results of the prospective BLISTER trial, the short-term response rates (≤3 blisters at 6 weeks) of our patients were comparable to those of the previous study by both per-protocol (patients under doxycycline without PSL) and intention-to-treat (all patients) analyses.[13] Furthermore, our patients under doxycycline treatment without PSL at 6 weeks showed significant decreases of BPDAI scores of both erosions/blisters and urticaria/erythema. These results suggest that doxycycline has short-term effectiveness in Japanese BP patients, especially with mild to moderate disease and no eosinophilia, and long-term safety.

Although some patients could be cured or managed for a long period with doxycycline alone, the majority of our patients initially treated with doxycycline required concomitant administration of PSL during the follow-up period. In the patients initially responded to doxycycline, however, the recurrent or mild remaining lesions could be controlled with relatively low-dose PSL in combination with doxycycline. Therefore, doxycycline might have a potential corticosteroid-sparing effect. From a practical point of view, short-term disease control with doxycycline may be beneficial during initial evaluation and management of comorbid diabetes,

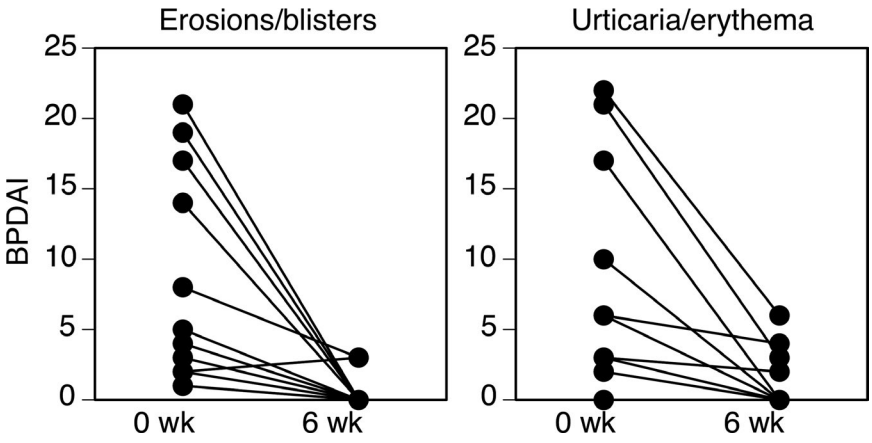

FIGURE 2 BPDAI at diagnosis and 6 weeks after doxycycline treatment without PSL. Mean (SD) BPDAI scores at 0 week and 6 weeks were 7.2 (7.3) and 0.4 (1.1) for erosions/blisters, respectively ($P = .005$); and 7.0 (7.7) and 1.1 (1.9) for urticaria/erythema, respectively ($P = .005$).

TABLE 3 Adverse events possibly related to doxycycline

Patient number	Adverse events	Interval from start of doxycycline to onset	Grade[a]	Discontinuation of doxycycline	Outcome
16	Increased AST Increased ALT	11 days	1	Yes	Recovered
25	Maculopapular rash	20 weeks	1	Yes	Recovered
27	Mucosal infection (oral candidiasis)	9 days	2	No	Recovered

Abbreviations:: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

hypertension, gastric ulcer, tuberculosis, and hepatitis virus infection before starting PSL. Alternatively, doxycycline may be used as an adjuvant or maintenance treatment after initial disease control with PSL.

The limitations of this study were the single-center retrospective design, small cohort mainly consisted of patients with mild to moderate disease, and commencement of PSL at the discretion of each physician rather than according to unified criteria. In Japan, tetracycline and minocycline have been widely used in BP, although only one small prospective randomized controlled trial comparing combination of tetracycline and nicotinamide with PSL has been conducted in the United States,[4] and for Japanese patients, only one case series of BP treated with combination of minocycline and nicotinamide was reported.[5] Our results suggest that doxycycline can be a safer treatment option for Japanese BP patients, because doxycycline appears to have similar effectiveness with a lower incidence of adverse events as compared with tetracycline or minocycline with or without nicotinamide.[4-9] In future, the efficacy and safety of doxycycline in Japanese BP patients should be confirmed in prospective randomized controlled trials of different tetracycline antibiotics.

ACKNOWLEDGMENTS

We thank Takashi Hashimoto, Norito Ishii, Wataru Nishie, Yuki Iwai, Mahoko Oginezawa, and Mami Nakajima for analyses of the serum autoantibodies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

APPROVAL OF THE RESEARCH PROTOCOL

This study has been approved by the ethics committee of Kido Hospital (approval number 19100312) and conforms to the provisions of the Declaration of Helsinki.

INFORMED CONSENT

As this study was a retrospective study, informed consent was obtained in the form of opt-out on the hospital website.

REGISTRY AND THE REGISTRATION NO

N/A.

ANIMAL STUDIES

N/A.

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How to cite this article: Kimura K, Kawai K. Doxycycline as an initial treatment of bullous pemphigoid in Japanese patients. *J Cutan Immunol Allergy*. 2020;3:80–85. https://doi.org/10.1002/cia2.12126