Baricitinib as a novel treatment for bullous pemphigoid: a case series report

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Short Report

Keywords: bullous pemphigoid, baricitinib, therapy effect, autoimmune bullous disease

Posted Date: March 6th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4002204/v1

Additional Declarations: No competing interests reported.

Baricitinib as a novel treatment for bullous pemphigoid: a case series report

Running title: Baricitinib in bullous pemphigoid treatment: a case series

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The work was done in China.

Abstract

Bullous pemphigoid (BP) is an autoimmune blistering disorder occurring mostly in the elderly. The standard treatment of BP patients with systemic corticosteroid have some potential serious side effects. Up till now, there is still lack of novel treatment for BP patients. Baricitinib, a selective Janus kinase (JAK) 1 and 2 inhibitor, has been used to treat rheumatoid arthritis, alopecia areata, and COVID-19. Successful treatment of refractory BP by JAK inhibitors has been reported in sporadic cases. In this study, we reported 8 BP patients treated with baricitinib. The patients after treatment were followed up for 3-24 months, with an average of 9.1 months. All 8 cases achieved disease control and the mean disease control period was 3 weeks (1-6 weeks). The bullous pemphigoid disease area index total (21.2 ± 13.0 to 2.5 ± 4.3, $p<0.01$), erosion/blister (6.0 ± 7.7 to 0.2 ± 0.5, $p<0.05$), urticaria/erythema (10.2 ± 11.9 to 0.0 ± 0.0, $p=0.06$), mucosal erosion/blister (10.0 ± 6.4 to 4.5 ± 5.1, $n=4$, $p=0.25$) and itching NRS (3.6 ± 3.5 to 0.0 ± 0.0, $p=0.06$) scores were all reduced after 2 months' treatment. Seven of 8 patients achieved complete remission during tapering at month 3 and did not experience relapse during the follow-up period. The serum levels of anti-BP180 autoantibodies (IgG) were reduced significantly (77.1 ± 47.8U/mL to 40.1 ± 37.1U/mL, $n=6$, $p<0.05$) after 3 months' treatment. During the follow-up period, only one patient experienced mild elevation of serum creatinine level after 3 months' treatment of baricitinib, which returned to normal through discontinuation of the medication. In conclusion, this study demonstrated that low-dose, short-term administration of baricitinib is effective and safe for treating BP patients.

Keywords: bullous pemphigoid, baricitinib, therapy effect, autoimmune bullous disease.

1 Introduction

Bullous pemphigoid (BP) is one of the most frequent autoimmune blistering diseases that predominantly affects elderly individuals, and the main symptoms are pruritic urticarial plaques and tense blisters [1]. The conventional treatments for BP are corticosteroids and immunosuppressive agents, which are limited by their adverse effects [2,3].

Baricitinib, a selective Janus kinase (JAK)1/JAK2 inhibitor, is used for treating rheumatoid arthritis, alopecia areata, and COVID-19, and has also been recommended for the treatment of psoriasis and other inflammatory-mediated diseases [4,5]. Based on existing case reports, there are three kinds of JAK inhibitors that are effective in treating BP, including tofacitinib (ten cases) [6-8], upadacitinib (two cases) [9,10] and baricitinib (one case) [11]. In addition, baricitinib has also been reported to be effective in the treatment of mucous membrane pemphigoid (two cases) [12,13] and epidermolysis bullosa pruriginosa (one case) [14]. Therefore, baricitinib may be effective for BP treatment.

In the present study, to investigate the efficacy and safety of baricitinib on BP, we reported 8 BP patients, who received baricitinib treatment, with detailed clinical and immunological results of 3-24 months' follow-up.

2 Materials and Methods

Materials and methods including patients, therapy and statistical analyses were shown in Appendix S1.

3 Results

3.1 Clinical and laboratory characteristics of BP patients

As detailed in Table 1, 8 BP patients treated by baricitinib were involved in this study, with an average age of 67.6 years old. At baseline, there were 4, 2 and 2 BP patients with only skin lesions, with only oral mucosa lesions, and with both skin and oral mucosa lesions, respectively. All 4 BP patients with oral mucosa lesions were negative for virus and fungal detection on the erosive surface of the oral mucosa. Before starting baricitinib treatment, 5 of the 8 BP patients experienced pruritus symptoms. The mean of bullous pemphigoid disease area index (BPDAI) total and mucosal erosions/blisters scores at baseline was 21.2 (n=8) and 10.1 (n=4), respectively.

For immunofluorescence detection, the positive rates of direct immunofluorescence for linear IgG and/or C3 deposition to basement membrane zone (BMZ) was 50.0% (2 of 4 cases); the positive rates of indirect immunofluorescence for linear IgG and/or C3 staining on BMZ was 100% (8 of 8 cases); and the positive rates of 1M-NaCl-split normal human skin by indirect immunofluorescence for IgG reactivity with the epidermal side of the split skin was 87.5% (7 of 8 cases).

By enzyme-linked immunosorbent assay, all the serum samples (8 cases) of BP patients were positive for anti-BP180 autoantibodies (IgG) at baseline (Table 1).

3.2 Response to baricitinib treatment

All patients after baricitinib treatment were followed up for 3-24 months, with an average of 9.1 months. All eight cases achieved disease control and the mean disease control period was 3 weeks (1-6 weeks). After two months' treatment, the conditions of all patients had significantly improved (Figure 1).

The BPDAI total (21.2 ± 13.0 to 2.5 ± 4.3, $p<0.01$), erosion/blister (6.0 ± 7.7 to 0.2 ± 0.5, $p<0.05$), urticaria/erythema (10.2 ± 11.9 to 0.0 ± 0.0, $p=0.06$), mucosal erosion/blister (10.0 ± 6.4 to 4.5 ± 5.1, n=4, $p=0.25$) and itching NRS (3.6 ± 3.5 to 0.0 ± 0.0, $p=0.06$) scores were all reduced after two months' treatment (Table 1). Seven out of 8 patients achieved complete remission during tapering at month 3, while the remaining one treated with a half-dose initial regimen of baricitinib showed improvement during the first three months of treatment, but got worse after the fourth months' treatment and switched to other treatments. All seven patients who responded well to baricitinib treatment did not experience relapse during the follow-up period. After 3 months' treatment, the serum levels of anti-BP180 autoantibodies (IgG) were reduced significantly (77.1 ± 47.8U/mL to 40.1 ± 37.1U/mL, n=6, $p<0.05$) (Table 1); however, the mean serum level of anti-BP230 autoantibodies (IgG) was elevated slightly (9.5U/mL to 18.2U/mL, n=3).

During the follow-up period, there were no severe adverse events occurred (Table 1). Only one patient experienced mild elevation of serum creatinine level (114.01 umol/L vs. normal range: 53-97 umol/L) after 3 months' treatment of baricitinib. This patient discontinued the baricitinib treatment and the serum creatinine level returned to normal.

4 Discussion

To our knowledge, there was only one report on BP patients treated with baricitinib previously [14]. In the present study, the main reasons for BP patients treated with baricitinib include (i) some patients cannot tolerate long-term or large-dose corticosteroid therapy due to underlying diseases and adverse events like osteoporosis, hypertension and diabetes; (ii) traditional treatment is ineffective; (iii) some patients refused to use corticosteroids therapy. For safety reasons, our exclusion criteria included past histories of malignant tumor, active or chronic infection and a high risk of thrombosis.

By the comparison of various BPDAI scores and serum autoantibodies (IgG) levels before and after treatment, it can be inferred that baricitinib can improve the conditions of BP patients including skin lesions, oral mucosal lesions and pruritus, and decrease the serum level of anti-BP180 autoantibodies (IgG). Especially for patient 5 and patient 6, after they were treated with dupilumab, there was only an improvement in the skin lesions, but no improvement in oral mucosal lesions. Upon discontinuation of dupilumab and initiation of treatment with baricitinib, significant improvement was observed in their oral mucosal lesions, while the skin lesions did not recur (Table 1 and Figure 1).

By comparing the efficacy of tofacitinib reported in previous literatures [6,7] with baricitinib in the present study, we found that there is no significant difference in disease control period between the two JAK inhibitors in treating BP (4.9 ± 8.36 weeks vs 3 ± 3.1 weeks, $p=0.131$); and both treatments can significantly reduce serum levels of anti-BP180 autoantibodies (IgG). Previous literatures reported that two old BP patients responded well and achieved complete remission with upadacitinib, another JAK inhibitor [9,10]. These results further supported that JAK inhibitors are effective for BP treatment.

The results of the present study and previous reports suggested that various JAK inhibitors can significantly improve the skin symptoms of BP patients [6-11]. However, there is still no reports on the effect of any JAK inhibitor on mucosal lesions of BP patients. In the present study, all 4 BP patients with oral mucosal involvement showed significant improvement in oral mucosal lesions after treatment with baricitinib. These results indicated that JAK inhibitors may be effective for treatment of oral mucosal lesions of BP patients.

Most frequently adverse events associated with JAK inhibitors include hypercholesterolemia, greater risk of thrombotic events, adverse events in pregnancy, cytopenias, acute renal injury, liver toxicity and malignancies [15]. In the present study, only one patient experienced mild elevation of serum creatinine level after 3 months' treatment of baricitinib, which returned to normal through discontinuation of the medication. Moreover, we did not observe those severe adverse events reported in previous literatures, indicating that treatment of BP with baricitinib might be a relatively safe therapeutic option. However, regular monitoring of adverse events is essential.

Limitations

The present study involved a relatively small number of BP patients using baricitinib treatment and the results may not be generalized to the entire BP patient population and should be confirmed by

larger case-controlled studies.

Conclusions

In conclusion, our study provides real-world practice evidence that low-dose, short-term administration of baricitinib is effective and safe for treating BP patients. Due to safety concerns, risk stratification, patient counseling, and adequate monitoring are essential.

Acknowledgments

This work was supported by the Scientific Research Project of Jiangsu Provincial Health Commission (ZD2021035) and National Key R&D Program of China (2022YFC3601800).

Competing Interests Statement

Authors declare no conflict of interests for this article.

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Supporting information

Appendix S1.

Figure legends

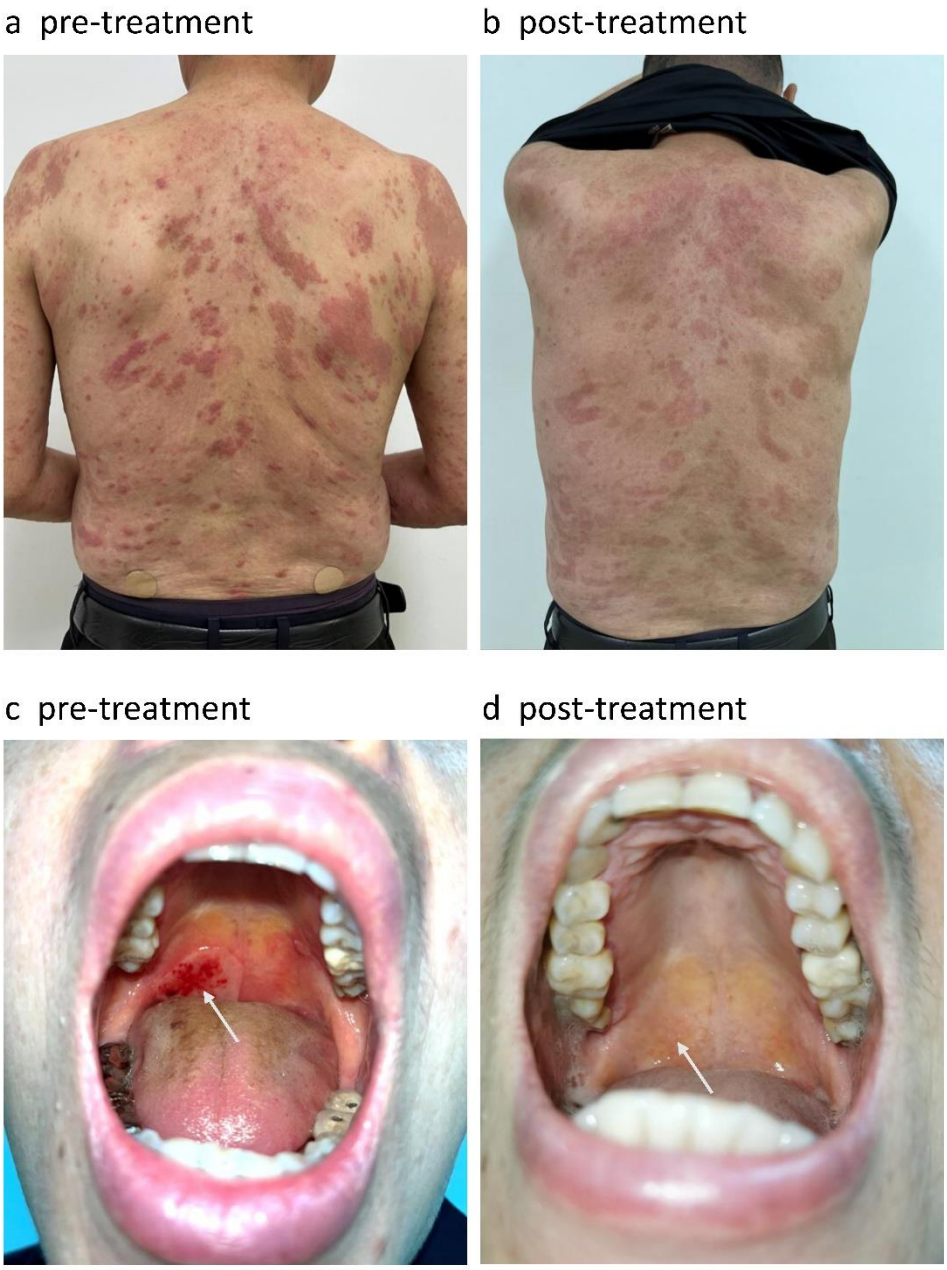
Figure 1. Clinical photographs of two BP patients who received baricitinib treatment.
(A, B) A and B showed the characteristics of admission (A) and after 4 weeks' treatment with baricitinib in patient 3 (B), respectively. (C, D) C and D showed the characteristic of admission (C) and after 8 weeks' treatment with baricitinib in patient 5 (D), respectively.

Table 1. Patient characteristics, medicine and disease course

Case No.	Age (years) / Sex	Disease duration before baricitinib treatment (months)	Onset	Systemic medications before baricitinib	Baricitinib dosage	Concomitant medications with baricitinib	Follow-up time (months)	BPDAI total scores		BPDAI erosion/blister scores		BPDAI erythema scores		BPDAI mucosal erosion/blister scores		BPDAI itching NRS scores		Serum levels of anti-BP180 autoantibodies (IgG) (U/mL)		Adverse events after the treatment of baricitinib
								pre	post	pre	post	pre	post	pre	post	pre	post	pre	post*	
1[a]	63/M	17	Relapse	Prednisone + Dupilumab	2 mg bid	Prednisone 10mg daily; tCS	3	5.3	0	1	0	4.3	0	0	0	3	0	55.4	30.8	None
2[a]	69/F	12	Relapse	Prednisone	2 mg bid	Prednisone 20mg daily; tCS	3	45	1	21	1	24	0	0	0	7	0	150	109.4	None
3[a]	51/M	19	Relapse	Prednisone	2 mg bid	Prednisone 25mg daily; tCS	17	31	0	1	0	30	0	0	0	9	0	50.1	15.9	None
4[a]	84/M	6	Relapse	Prednisone	2 mg qd	tCS	7	20	0	3	0	17	0	0	0	5	0	150	Unkno-wn	None
5[b]	58/F	4	Initial	Dupilumab	2 mg bid	None	6	12.3	6	0	0	0	0	12.3	6	0	0	75.3	53.6	None
6[b]	60/F	7	Initial	Dupilumab	2 mg bid	None	9	11	0	0	0	0	0	11	0	0	0	72	Unkno-wn	Elevation of serum creatinine level (114.01 umol/L vs. normal range: 53-97 umol/L)
7[c]	79/F	8	Relapse	Minocycline	2 mg bid	tCS	24	17	1	9	0	6	0	2	1	5	0	32.5	18.7	None
8[c]	77/M	3	Initial	Dupilumab	2 mg qd	tCS	4	29.3	12	13.3	1	0	0	16	11	0	0	31.1	12.3	None

[a], with only skin lesions; [b] with only oral mucosal lesions; [c], with both skin and oral mucosal lesions; M, male; F, female; bid, twice a day; qd, once a day; tCS, topical corticosteroid; BPDAI, bullous pemphigoid disease area index; pre, before administration of baricitinib; post, after 2 months' treatment of baricitinib; post*, after 3 months' treatment of baricitinib; IgG autoantibodies against BP180 NC16A were measured by MBL, Nagoya, Japan according to the manufacturer' instruction and the cut-off values in serum samples were 9 U/mL.

Figure 1



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Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixS1.pdf