

# Evaluation of methotrexate and its influence on serum autoantibodies against BP180 in patients with bullous pemphigoid: a pilot study

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## Dear Editor,

Bullous pemphigoid (BP), the most common subepidermal autoimmune blistering disease, is characterized by the presence of autoantibodies directed against components of the skin basement membrane zone or, specifically, against two hemidesmosomal antigens: BP180 and BP230. It is largely identified through the highly sensitive and specific enzyme-linked immunosorbent assay (ELISA) for the detection of autoantibodies against BP180 (BP180 Ab) (1–3). Even though superpotent topical corticosteroids (TCS) are the first-line treatment (4), in our experience this therapeutic regimen is not satisfactory due to difficulties in nursing care, as well as side effects. Some authors have proposed methotrexate (MTX) as a key adjuvant and steroid-sparing agent in the management of BP; however, evidence regarding its impact on serum BP180 Ab levels remains limited (5–11).

To address this gap, we conducted a pilot study involving nine BP patients treated consecutively at our dermatology unit between January 2020 and January 2025, specifically evaluating the effect of MTX on BP180 Ab titers. BP diagnosis was established based on histology, direct immunofluorescence, and the detection of circulating BP180 Ab through ELISA. Exclusion criteria included former immunosuppressive treatments in the previous 4 weeks and contraindication to MTX therapy. All patients initially received oral corticosteroids (CS) at a dose of 0.5 mg/kg/day until disease control (i.e., absence of new blisters for 3 consecutive days) was achieved. Upon clinical stabilization, 15 mg of subcutaneous MTX weekly was introduced as a steroid-sparing agent in addition to folic acid supplementation (5 mg the day after injection). CS were tapered according to disease control, with a reduction of 5 mg per week until discontinuation, when feasible. MTX tapering was subsequently attempted while maintaining subcutaneous administration, either by reducing the weekly dose or by increasing the interval between administrations.

Patients were instructed to use TCS for isolated prodromal or bullous lesions. Relapse was defined as the occurrence of  $\geq 3$  new bullae per week and was treated with systemic corticosteroids. BP180 Ab were tested at the moment of: i) diagnosis, ii) disease control achieved through steroid therapy / introduction of MTX,

iii) interruption of steroid therapy, and iv) decision whether MTX could be suspended. Four men and five women were included in the study. The average age was  $79.1 \pm 11.5$  years, and the mean follow-up period was  $3.4 \pm 1.7$  years.

At baseline, BP180 Ab levels were heterogeneous. All patients achieved disease control with systemic CS (Table 1). At this stage, only a modest overall reduction in BP180 Ab levels was observed (–6.9%), with three patients paradoxically exhibiting increased titers (+48.1%). Following disease control, MTX was initiated in all patients. Two discontinued treatment after a single MTX injection due to adverse events (liver cytolysis and anemia, respectively) and so seven patients continued the CS + MTX therapy. CS therapy was discontinued in six of the seven remaining patients; however, two required reintroduction of CS due to disease relapse. A moderate BP180 Ab reduction was observed in five patients (–22.7%) and two showed increases (+13.3%). Four patients continued the MTX monotherapy, with a further BP180 Ab decline noted (–18.2%), although two presented mild increases (+6.2%). Notably, patient 7 experienced a cumulative reduction of 80% from baseline under MTX alone, correlating with sustained clinical remission. Conversely, in patients 5 and 6 the antibody levels rose despite disease control. This suggests a possible uncoupling between serologic markers and clinical activity, in contrast to previous findings in the literature (3, 12).

The Pearson correlation between variables was weak at both the diagnosis and in the pre-MTX phase ( $R = 0.0606$ ). Analysis of variance (ANOVA) comparing pre- and post-treatment antibody levels yielded a non-significant  $p$  (0.193). CS alone failed to consistently reduce antibody titers, whereas MTX introduction was more likely to induce significant declines, especially upon CS tapering (Table 2).

Although MTX has been used as monotherapy for BP, the data reported here suggest that this drug may contribute to the modulation of autoantibody production. However, studies involving a larger patient cohort are required to achieve statistical significance. This pilot investigation provides a rationale for further research to determine whether autoantibody titers may serve as biomarkers of treatment response in BP patients treated with MTX.

**Table 1** | Effects of systemic corticosteroid and methotrexate on disease activity and autoantibodies against BP180 (cutoff ≥ 20 UA).

Patient	Sex	Age	Variable	Therapy stage				Last FU
				None (diagnosis)	CS (disease control)	CS + MTX (stop CS)	MTX (stop MTX)	
1	F	84	DA	2	0	—	—	—
			Ab	95	75	—	—	—
			Δ (%)		-21.0			
2	F	88	DA	2	0	0	—	2 <sup>†</sup> , <sup>‡</sup>
			Ab	164	101	85	—	120
			Δ (%)		-38.4	-48.2		-26.8
3	F	92	DA	2	0	—	—	—
			Ab	22	23	—	—	—
			Δ (%)		+4.5			
4	F	65	DA	2	0	0	—	0 <sup>‡</sup>
			Ab	152	124	67	—	55
			Δ (%)		-18.4	-55.9		-63.8
5	F	93	DA	1	0	0	—	0 <sup>‡</sup>
			Ab	33	58	46	—	38
			Δ (%)		+75.8	+39.4		+15.1
6	M	61	DA	2	0	0	—	0 <sup>‡</sup>
			Ab	75	123	135	—	87
			Δ (%)		+64.0	+80.0		+16.0
7	M	71	DA	1	0	0	0	0 <sup>*</sup>
			Ab	85	25	21	17	17
			Δ (%)		-70.6	-75.3	-80.0	-80.0
8	M	77	DA	1	0	0	—	0 <sup>‡</sup>
			Ab	48	37	25	—	28
			Δ (%)		-22.9	-47.9		-41.7
9	M	81	DA	1	0	0	0	0 <sup>†</sup>
			Ab	160	104	121	64	51
			Δ (%)		-38.1	-27.9	-60.0	-68.1

CS = corticosteroid, MTX = methotrexate, FU = follow-up, M = male, F = female, DA = disease activity (0: no blisters; 1: 1–10 blisters; 2: > 10 blisters), Ab = antibodies. At last follow-up: \*no therapy, †topical CS, ‡MTX.

**Table 2** | Percentage change in antibodies against BP180 before, during, and after therapy with methotrexate.

Patient	Diagnosis Ab 180 (U/ml)	Pre MTX Δ Ab 180 (%)	Stop CS Δ Ab 180 (%)	Stop MTX Δ Ab 180 (%)
1	95	-21.0	—	—
2	164	-38.4	-48.2	—
3	22	+4.5	—	—
4	152	-18.4	-55.9	—
5	33	+75.8	+39.4	—
6	75	+64.0	+80.0	—
7	85	-70.6	-75.3	-80.0
8	48	-22.9	-47.9	—
9	160	-35.0	-24.4	-60.0

Ab = antibodies, CS = corticosteroid, MTX = methotrexate.

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