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LETTER TO THE EDITOR

Pemphigus foliaceus treated with minocycline monotherapy or low-dose prednisolone combination therapy

Dear Editor,

Pemphigus foliaceus (PF) is a classic form of pemphigus, mainly mediated by anti-Desmoglein 1 (Dsg1) antibodies (1). Patients often present with scaly cutaneous erosions and fragile vesicles on an erythematous base, with neutrophils and/or eosinophils infiltrated within superficial dermis in pathology. Systemic or topical corticosteroid (s/tCS) combined with immunosuppressive agents is the standard therapy. However, steroid accumulation would bring side effects, exacerbating patients' already impaired quality of life. Pemphigus especially requires a long view, so it is necessary to find a way to achieve both long-term remission and minimize toxicities.

This was a retrospective analysis conducted on 36 PF patients in the active stage over 5 years (from June 2016 to June 2021) at Peking University First Hospital under National Clinical Research Center for Immune and Skin Diseases of China. All patients met the diagnostic criteria (2) and were treated with minocycline (150 ~ 200 mg qd) monotherapy or combined with low-dose prednisolone (<20 mg daily) according to clinical severities and informed patient preference. Baseline data before minocycline use were collected regarding age, gender, comorbidity, titre of anti-Dsg1 antibody, disease duration, previous therapy, and clinical severity defined by Pemphigus Disease Area Index (3) (Table 1).

Among 23 males and 13 females, 47.2% of patients had comorbidity before the use of minocycline. Hypertension (9, 52.9%) and diabetes mellitus (3, 17.6%) ranked top two. There was no significant difference in disease severity between the two treatment arms. The mean duration of the disease before minocycline administration was 17.7 (11.5, 23.5) months, with an average level of anti-Dsg1 antibody being 133.63 (88.78, 199.26) U/ml.

Twenty-five patients (69.4%) responded with disease control (DC) within 3 months, with 11 patients completely controlled on minocycline alone (Table 2). Once the patient reached DC state (4), tapering would be initiated. Eleven patients partially responded (PR), with transient lesions or minor flares (predominately 0 ~ 2 erosions) necessitating the intermittent use of topical clobetasol 10 ~ 15 g/w. According to Joly et al. (5), the topical dose of 5 ~ 10 g/w is too small to consider its influence on the overall efficacy. By 6 months, 66.7% of patients achieved complete remission (CR), and 14 were in the combined therapy arm. Interestingly, patients who reached CR within half a year were the same as those who achieved DC within 3 months. We suspected that those patients themselves respond better to minocycline, as whose pathogenic antibodies significantly decreased when the disease status switched (Baseline-DC, $p = .001$; DC-CR, $p < .001$). Of the patients who reached DC or CR at a slower rate, four (33.3%) remained in high Dsg1-specific autoantibody state even at the last follow-up. One high-autoantibody,

Table 1. Characteristics of the patients included in the study.

	Treatment arms		
	Monotherapy $N = 15$	Combined therapy $N = 21$	p Values
Mean age ± SD, years	62.8 ± 5.9	64.1 ± 8.4	.923
Gender, male/female	9/6	14/7	.518
Comorbidity primary/secondary	53.3%	42.9%	.562
Hypertension	2/3	3/1	
Diabetes mellitus	0/1	1/1	
Others*	0/2	1/3	
Baseline anti Dsg1 titre** (U/ml) M(Q_1, Q_3)	130.85 (85,73, 193.63)	135.61 (92.50, 192.75)	.965
Disease duration before minocycline using (months) M(Q_1, Q_3)	15.5 (10.0, 19.0)	19.3 (12.0, 26.0)	.154
Previous treatment			–
sSC	8	15	
tSC	12	20	
Azathioprine	8	18	
Methotrexate	6	12	
Cyclosporine	3	9	
Clinical severity			.856
Mild	8	10	
Moderate	6	10	
Severe	1	1	

Statistical analysis was performed using an independent-sample t-test for continuous variables or a two-tailed Chi-square test for categorical variables.
Others*: secondary cataract (2), secondary peptic ulcer (1), primary renal dysfunction (1) and secondary osteopenia (1) respectively.
**Anti-Dsg1 antibody was tested by the ELISA kit of Euroimmune Company, the cut-off value is 20.0 U/ml.
SD: standard deviation.

Table 2. Treatment response of PF patients treated with apremilast.

	Treatment arms		
	Monotherapy $N = 15$	Combined therapy $N = 21$	p Values
Time to DC (weeks) M(Q_1, Q_3)	18.3 (12, 18)	19.2 (12, 28)	.825
Frequency of DC at third month	11/15	14/21	.769
Anti-Dsg1 antibody titre at DC (U/ml) M(Q_1, Q_3)	100.28 (48.66, 128.33)	103.82 (72.4, 150.32)	.852
Time to CR (months) M(Q_1, Q_3)	7.2 (5.3, 7.5)	9.7 (6.0, 15.0)	.124
Frequency of CR at sixth month	10/15	14/21	.773
Anti-Dsg1 antibody titre at CR (U/ml) M(Q_1, Q_3)	38.69 (19.08, 37.79)	44.12 (24.62, 56.01)	.604
Treatment-related adverse effects	Pigmentation (2)	Tinea corporis (1) Pigmentation (2)	–
Treatment duration (months) M(Q_1, Q_3)	10.7 (8.0, 11.5)	11.9 (8.0, 17.0)	.482
CR off at last follow-up	3/15	3/21	–

Statistical analysis was performed using an independent-sample t-test for continuous variables or a two-tailed Chi-square test for categorical variables.
SD: standard deviation; DC: disease control; CR: complete remission; NS: not significant.

moderate PF female who took monotherapy relapsed after 1-year DC and then switched to rituximab infusion. Luckily, none of the other three relapsed under CR on therapy (prednisolone 5–10 mg daily). In the 20th month, 35 patients (97.2%) reached CR. And there is no magnificent difference in the time to DC or CR between mild and moderate PF patients ($r = 0.217$, $p = .542$; $r = -0.039$, $p = .811$, Spearman's rho correlation analysis).

Over a 3-year follow-up, two severe patients experience several mild new activities; one kept high level of anti-Dsg1 antibody. With topical clobetasol 5 g qw, the rashes would last less than 2 weeks. And they were still given CR on therapy to prevent flares.

Medication side effects noted in those patients included tinea corporis ($n = 1$) and minocycline-related generalized hyperpigmentation of the skin and/or gingiva ($n = 4$) (Table 2). There were no severe adverse events occurred or primary contraindications worsen that limited minocycline and low-dose prednisolone treatment (6,7).

The treatment of pemphigus mainly includes s/tCS, accompanied by immunosuppressor (1). The use of tetracycline, doxycycline, or minocycline plus niacinamide (TCN/NAM) has proven a successful treatment regimen, inhibiting the infiltration of lymphocytes and neutrophils in the lesion of bullous pemphigoid (8). On the other hand, tetracyclines have the effect to bind calcium ions. Theoretically, they may occupy the calcium-dependent binding site for anti-Dsg antibodies and alleviate the formation of epidermal blisters caused by the immune response. Still, it has been less supported in the treatment of pemphigus. Chaffins et al. (9) reported 11 patients (5 CR, 4 PR, 2 nonresponders) under TCN/NAM in 1993, and Alpsoy et al. (10) reported 10 patients (2 CR, 3 PR, and 5 nonresponders) in 1995. McCarty and Fivenson (11) reported a retrospective study of pemphigus patients using TCN/NAM with sCS (1–2 mg/kg/d), showing successful outcomes in the management of active pemphigus. However, the steroid accumulation was rather high.

Since 2016, we have applied minocycline monotherapy and combination therapy with low-dose prednisolone to treat PF, which successfully cured most patients and reduced the titre of pathogenic antibodies without serious drug-related adverse reactions. The efficacy, adverse reactions, and patient prognosis in the long run should be evaluated in prospective multi-centre studies with a large sample size in the future.

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