CASE STUDY

Efficacy of combination therapy of steroid and methotrexate for refractory pemphigus

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Abstract

The first line of treatment for pemphigus is systemic corticosteroids. When steroids alone do not result in remission, additional immunosuppressants are recommended. Twenty-two patients with pemphigus vulugris were treated with steroids and other immunomodulators. However, they were refractory, and hence, methotrexate (MTX) was administered. The efficacy of MTX was assessed for 16 patients who were able to continue MTX therapy for 1 year. Steroid dose reduction was possible in 11 patients. One patient with severe infections had diabetes and was elderly. Our results suggested that MTX was useful as a steroid-sparing agent in treating recalcitrant pemphigus, when an initial immunosuppressant treatment had failed. However, adverse effects should be closely monitored.

KEYWORDS
desmoglein, methotrexate, pemphigus, prednisolone, steroid

1 | INTRODUCTION

Methotrexate (MTX) is a folate antagonist for the treatment of malignancies[1] and is used in non-neoplastic diseases as an immunosuppressive agent.[2,3] In the guidelines for pemphigus treatment, steroids are mentioned as the first choice, and the efficacy of MTX in combination has already been reported.[4–12] Recently, the British guidelines have positioned MTX as the third-line treatment following the second-line treatment with azathioprine and mycophenolate mofetil.[13,14] In Japan, guidelines for pemphigus treatment indicate that MTX is effective in reducing steroid use.[15] However, reports on the efficacy of MTX in treating pemphigus in Japan are limited.

Because steroids alone do not lead to remission in many cases, the combined use of an immunosuppressant can be considered. We have encountered patients with relapsing diseases or adverse effects even after several types of immunomodulators were administered. Therefore, we evaluated the efficacy and safety of oral MTX in 16 patients who were able to continue MTX therapy for 1 year of 22 patients with pemphigus vulgaris who were refractory to the treatment with steroid and other immunomodulators and who were added MTX.

2 | CASE SERIES

A retrospective chart review was performed on patients with pemphigus vulgaris who enrolled in our hospital between 2007 and 2019.

The inclusion criteria were as follows: (i) patients treated with oral MTX for pemphigus at our institutions and (ii) a diagnosis of pemphigus vulgaris based on (a) clinical presentation consistent with pemphigus (blistering and erosions of mucosal or cutaneous surfaces or both), (b) skin biopsy demonstrating suprabasilar acantholysis, or

(c) characteristic findings by either direct immunofluorescence performed on skin biopsy specimens (i.e., deposits of IgG in the epidermis) or serological demonstration of anti-Desmoglein (Dsg)1 or 3 antibodies by enzyme-linked immunosorbent assay (ELISA) or chemiluminescent enzyme immunoassay (CLEIA). Anti-Dsg1 or 3 antibody titers were measured using CLEIA (STACIA MEBLux™ test Dsg1/3, MBL laboratories, Nagoya, Japan) after December 2013 and before that, using ELISA (MESACUP™-2 Dsg1/3, MBL). Patients taking other nonsteroidal immunomodulators at the time of MTX initiation were included as long as the treatment remained unchanged for more than 3 months. The 22 patients included in this study were first treated with prednisolone (PSL), followed by another immunosuppressant prior to the start of MTX administration. The administration of MTX was initiated to reduce patients' dependence on systemic glucocorticoids (steroids). In all patients, the initial dose of MTX was 2–4 mg/wk with increment of 2 mg depending on the therapeutic response, until reaching a maximum dose of 4–12 mg/wk. In addition, all patients receiving MTX were prescribed folic acid at a dose of 5 mg/wk. The patients in whom pemphigus vulgaris was controlled after the inclusion of MTX, the dose of PSL or other nonsteroidal immunomodulators was attempted to reduce.

Data collected from each patient included a history of previous treatment with immunomodulators other than MTX, anti-Dsg antibody titers, pemphigus disease area index (PDAI) score, and dosing of MTX and PSL at each visit. The PDAI score was calculated according to the recommendations of the International Pemphigoid Committee[16-18]; the scores range from 0 to 263. Two groups were compared using paired Student's t-test. Fisher's exact test was used to compare the categorical data. Results with $p < 0.05$ were considered statistically significant.

A total of 22 Japanese patients met the criteria for inclusion in this study (Table 1). The mean time from diagnosis to initiation of MTX therapy was 37.7 ± 35.5 months (range: 4–154 months, median: 23.5 months). Prior to the start of MTX therapy, PSL was combined with other immunomodulators; mizoribine was the most used immunomodulator, followed by azathioprine and cyclosporine. Efficacy was evaluated in 16 patients who were able to continue MTX therapy for 1 year (Figure 1a).

In these 16 patients in whom MTX therapy was initiated, the mean dose of PSL at the time of initiation was 0.37 ± 0.19 mg/kg/d (range: 0.23–1.02 mg, median: 0.30 mg). The mean time from diagnosis to initiation of MTX therapy was 38.3 ± 36.2 months (range: 4–154 months, median: 25 months). The mean maximum dose of MTX for each patient was 8.1 mg/wk (range: 6–12 mg/wk).

In 15 patients (68.2%), systemic corticosteroid dose could be reduced (Table 2). However, in all these patients, PSL could not be completely withdrawn. The average dose of PSL required to control symptoms of pemphigus was 0.24 mg/kg/d (range: 0.16–0.49 mg/kg/d) 1 year after the initiation of MTX therapy, which corresponds to 63.8% PSL dose reduction on an average, and this reduction was

TABLE 1 Characteristics of the patient with pemphigus vulgaris (n = 22) enrolled in this study

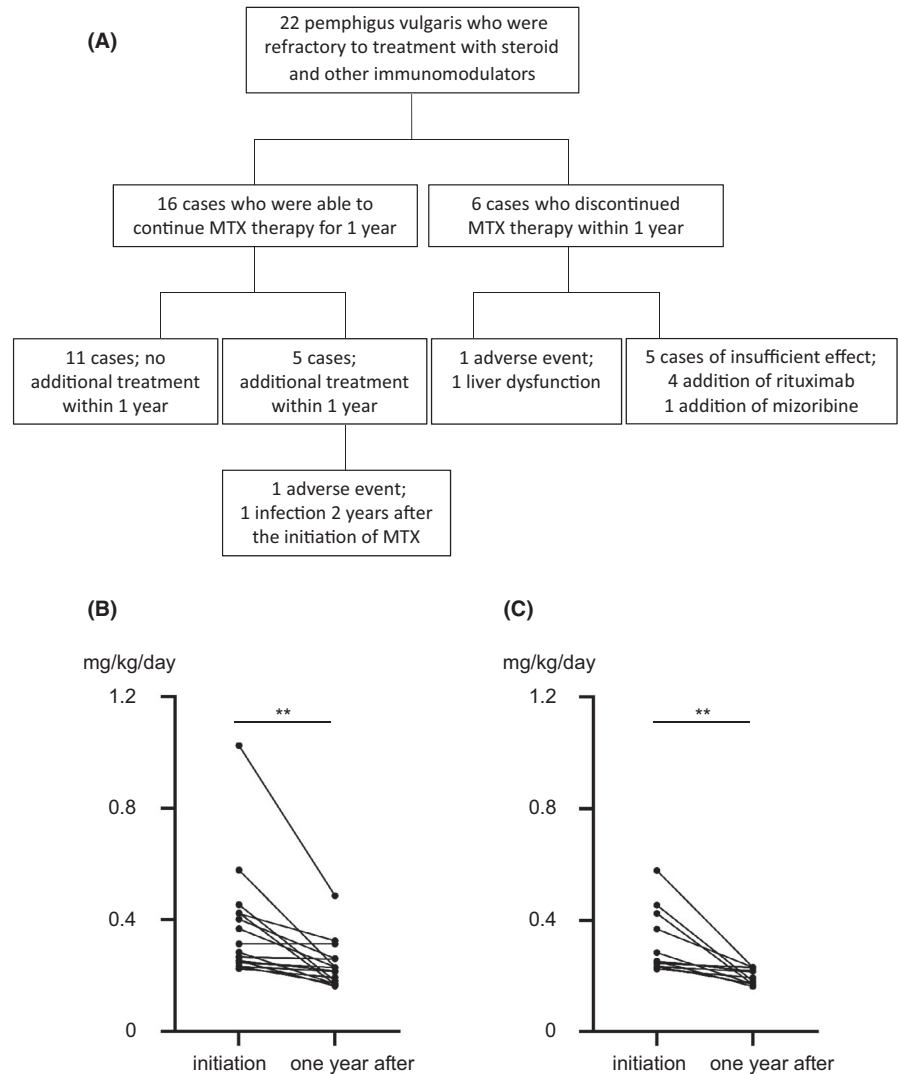| Characteristics	Observations
Age at initiation of MTX therapy, years	
Mean ± SD	53.0 ± 10.0
Sex, n (%)	
Female	12 (54.5%)
Male	10 (45.5%)
Anti-Dsg1 antibody titer at initiation of MTX therapy, U/mL [†]ELISA (n = 2)	730.0 ± 150.0
Anti-Dsg3 antibody titer at initiation of MTX therapy, U/mL [†]ELISA (n = 5)/[‡]CLEIA (n = 15) Mean ± SD	207.6 ± 222.3/364.9 ± 339.0
PDAI at initiation of MTX therapy	
Mean ± SD	7.2 ± 12.2
Immunomodulators used before MTX (n = 37)[*]	
Mizoribine, n	16
Azathioprine, n	11
Cyclosporine, n	9
Mycophenolate mofetil, n	1
Mean maximum dose of MTX, mg/wk (range)	7.6 (4–12)
Mean dose of PSL at initiation of MTX, mg/kg/d (range)	0.37 (0.23–1.02)
Discontinuation due to adverse event, n (%)	2 (9.1%)

Abbreviations: Dsg, desmoglein; MTX, methotrexate; PDAI, pemphigus disease area index; PSL, prednisolone.

[†]Anti-Dsg1/3 antibody titer, using enzyme-linked immunosorbent assay (ELISA) (Dsg1, Cutoff < 14.0; Dsg3, Cutoff < 7.0).

[‡]Anti-Dsg3 antibody titer, using chemiluminescent enzyme immunoassay (CLEIA) (Cutoff < 20.0).

[*]There is some overlapping.

FIGURE 1 (A) Flow chart of the patients enrolled in this study. (B) Mean dose of prednisolone at initiation and 1 y after initiation of methotrexate (**p < 0.01; paired *t*-test). Continue MTX therapy for 1 y (*n* = 16). (C) Mean dose of prednisolone at initiation and 1 y after initiation of methotrexate (**p < 0.01; paired *t*-test). No additional treatment (*n* = 11)

(A)

22 pemphigus vulgaris who were refractory to treatment with steroid and other immunomodulators

16 cases who were able to continue MTX therapy for 1 year

6 cases who discontinued MTX therapy within 1 year

11 cases; no additional treatment within 1 year

5 cases; additional treatment within 1 year

1 adverse event; 1 liver dysfunction

5 cases of insufficient effect; 4 addition of rituximab 1 addition of mizoribine

1 adverse event; 1 infection 2 years after the initiation of MTX

(B)

mg/kg/day

initiation   one year after

(C)

mg/kg/day

initiation   one year after

statistically significant (*p* = 0.0024) (Figure 1b). In five of the 16 patients, three cases of steroid increase and two cases of rituximab introduction were included within 1 year after the initiation of MTX administration. Thus, only 11 patients who did not add another treatment were evaluated and the average dose of PSL required to control symptoms of pemphigus was 0.20 mg/kg/d 1 year after the initiation of MTX therapy, which corresponds to 61.2% PSL dose reduction on an average, and this reduction was statistically significant (*p* = 0.0048) (Figure 1c). In 16 patients, the mean PDAI at the start of oral MTX administration was 5.8 ± 11.1. One year after starting MTX treatment, the mean PDAI was 0.38 ± 0.36. In 13 patients, the antibody levels a year after the start of MTX treatment decreased 162.3 U/mL in average compared with that of the baseline. In six patients who discontinued MTX within 1 year, the average dose of PSL at the time of discontinuation of MTX was 0.45 mg/kg/d.

In 2 of 22 (9.1%) patients, adverse events occurred. One month after the initiation of MTX administration, mild liver dysfunction occurred in a patient. Another patient who was elderly with relapsing pemphigus died of scabies and sepsis 2 years after the initiation of MTX administration. The case with infectious diseases had diabetes.

The age at the start of MTX therapy in the patient who had infections was 70 years old, which was higher than the mean age of the 22 patients (53.0 years). In this study, no patients had adverse events such as interstitial pneumonia or leukopenia.

3 | DISCUSSION

There have been some reports on the effectiveness of MTX therapy for pemphigus. A total of seven studies on MTX administration in patients with pemphigus were reviewed, and it was found that among 136 patients, 111 patients (82%) showed clinical improvement when treated in combination with steroids.[10] Furthermore, administration of MTX (15 mg/wk) in 30 patients with pemphigus ameliorated the severity of the disease in 21 (84%) of 25 patients with severe to moderate disease.[11] Additionally, mean MTX administration (18.9 mg/wk) in 23 patients with pemphigus improved clinical findings in 21 patients (91%). Overall, in 16 patients (70%), PSL was completely discontinued. The average time from the initiation of MTX therapy to discontinuation of PSL was 17.6 months.

	Continue MTX therapy for 1 y (n = 16)[*]	No additional treatment (n = 11)
Improvement in PDAI, n (%)	6 (27.3%)	4 (18.2%)
Partial steroid-sparing effect, n (%)	15 (68.2%)	11 (50.0%)
PSL at initiation of MTX, mg/kg/d (range) ± SD	0.37 (0.23–1.02) ± 0.17	0.32 (0.23–0.58) ± 0.25
PSL 1 y after the start of MTX therapy, mg/kg/d (range) ± SD	0.24 (0.16–0.49) ± 0.080	0.20 (0.17–0.23) ± 0.026
Improvement in antibody titer[†], n (%)	9/18 (50.0%)	7/18 (38.9%)

TABLE 2 Treatment response in pemphigus vulgaris patients (n = 22)

MTX, methotrexate; PDAI, Pemphigus disease area index; PSL, prednisolone.

*Six of 22 patients discontinued MTX within 1 y.

[†]The change in antibody titer was tracked in 18 of the 22 cases.

Adverse effects were observed in two patients (9%) with anemia and liver dysfunction.[12]

Reports from Japan on the treatment of pemphigus using MTX are limited. In this study, patients who were refractory to treatment with other immunomodulators in addition to PSL received an average of 7.6 mg/wk of MTX for 1 year, which resulted in a reduction in steroid dosage in 15 of 22 patients (68.2%). The 11 patients who did not add another treatment other than MTX were also able to reduce their steroid doses in all cases. In these cases, the PSL dose was significantly reduced 1 year after the initiation of MTX administration. Despite the fact that MTX usage in Japan was lower than that reported abroad, this study also found cases of lower steroid doses, lower antibody titers, and improved symptoms. Considering these results, it may be possible to expect an effect with MTX therapy even if initial treatment with immunosuppressants, which is the second-line in addition to steroids, failed.

One of the 22 patients who developed serious infections was elderly and had diabetes. It has been reported that the immunosuppressive effect of MTX therapy in rheumatoid arthritis increases the infection rate and the severity of infection, especially in patients with diabetes and those on steroids.[19–21]

In conclusion, MTX is useful as a steroid-sparing agent in recalcitrant pemphigus after the treatment with first nonsteroidal immunosuppressant has failed. It is necessary to pay attention to the infection profile, especially, in elderly diabetic patients. Therefore, careful follow-up is required when using MTX in combination with PSL, as some patients may develop severe infections during the course of the therapy.

4 | DECLARATION SECTION

Approval of the research protocol: The study was approved by the Institutional Review Board of Yokohama City University.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: Approval number: B200400014.

Animal Studies: N/A.

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