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Maintenance of Remission after Oral Metronidazole Add-on Therapy in Rosacea Treatment: A Retrospective, Comparative Study

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Background: Rosacea is a chronic inflammatory disease which requires treatment to maintain remission.
Objective: Recently, the effect of *Demodex* mites in recurrence of rosacea has been described. Although there is limited data, previous reports have suggested that oral metronidazole demonstrated efficacy in treatment of rosacea.
Methods: Fifty-eight Korean patients with rosacea who received treatment with oral minocycline (50 mg twice daily) only or with two-week of oral metronidazole (250 mg thrice daily) were evaluated retrospectively. Their responses were evaluated by Investigator's Global Assessment (IGA), Clinician's Erythema Assessment (CEA), and patient's Global Assessment. The recurrence rate and odds ratio of risk factors for recurrence were also estimated.
Results: The combination treatment group reported earlier clinical improvement and lower mean IGA and CEA than the monotherapy group. Approximately 48% of patients with combination treatment did not show relapse within 24 weeks, which is significantly higher than that in the monotherapy group (p=0.042).
Conclusion: Add-on therapy of oral metronidazole appeared to be a significant protective factor for recurrence of rosacea (p<0.05). This study suggests that oral metronidazole can be added to oral minocycline to reduce relapses in rosacea patients with tolerable safety.

Keywords: Metronidazole, Minocycline, Rosacea

INTRODUCTION

Rosacea is a chronic inflammatory skin disorder that mainly affects the central face, characterized by erythema, telangiectasia, edema, or papulopustules. The reported prevalence of rosacea ranges from 1% to 20%[1]. Although the pathophysiology of rosacea remains to be elucidated, immunologic alterations and neurovascular dysregulation are considered to play important roles in initiating and strengthening the clinical manifestations of rosacea. Various triggering factors including *Demodex* colonization, microbial stimuli, ultraviolet radiation, heat, and stress are considered to be related to the initiation or aggravation of rosacea[2,3].

Tetracyclines such as tetracycline, doxycycline, and minocycline, have been the mainstay systemic oral therapy for rosacea. Minocycline was previously reported as noninferior to doxycycline in rosacea treatment in terms of efficacy with comparable safety[4].

Treatment of rosacea is still challenging due to its frequent relapses. Although there is limited data, oral metronidazole demonstrated efficacy in patients with rosacea[5-8]. Mechanism of metronidazole action in rosacea had been suggested as anti-inflammatory effects and anti-parasitic activity on *Demodex folliculorum*[9-11]. Recently, the effect of *D. folliculorum* in increasing the duration of rosacea and probability of recurrence has been described[12]. There have been few reports of systemic

metronidazole therapy for *Demodex*-associated diseases including rosacea and Demodicidosis[5-8,13-15], which encouraged us to investigate whether the early combination use of oral metronidazole with minocycline could induce rapid resolution and prevention of relapse of rosacea. The objective of this study was to evaluate the real-world efficacy and safety of oral metronidazole add-on treatment with minocycline in maintaining remission of rosacea.

MATERIALS AND METHODS

Study design

We conducted a retrospective chart review of electronic medical records of patients diagnosed with rosacea and treated with oral minocycline with or without metronidazole. The data were provided by the Department of Dermatology at Ulsan University Hospital in Korea. The study was approved by Ulsan University Hospital's Institutional Review Board (UUH-IRB-2019-02-030). Initial survey data with baseline and interim efficacy assessments including photographs, outpatient records, and telephone interviews were obtained for each patient. Informed consent was obtained for using photographs and outpatient records.

All patients completed the initial questionnaires. The questionnaire was used to assess family history, associated diseases, and various triggering factors. Single scrape (squeezing) test using potassium-hydroxide (KOH) preparation were conducted in 54 patients. While most of the studies define more than 5 *Demodex* mites count seen in standardized skin surface biopsy (SSSB), we defined test positive as 5 or more *Demodex* mites seen at 100× magnification of microscope done by single scraping or squeezing of 2 to 3 inflammatory papules or erythematous lesion. Interim photographs were obtained when available, and those without photographs were excluded from the efficacy assessments of Investigator's Global Assessment (IGA) and Clinician's Erythema Assessment (CEA). Patients were considered as lost to follow-up if they had not visited the clinic for more than three months after the last visit and assessed efficacy through telephone interview.

Study population

Patients had to meet the following criteria to be included in the study: clinical diagnosis of rosacea assessed by dermatologists; prescribed minocycline with or without metronidazole between January 2014 and February 2019 at the department of dermatology of Ulsan University Hospital, Korea; age of at least 18 years; and had a score of >1 on IGA or ≥1 on CEA. We excluded patients who had other dermatoses that might interfere with rosacea or the evaluation of treatment results.

Eligible patients were categorized into two therapy groups based on their treatment. In monotherapy group, the patients were treated with only 50-mg oral minocycline twice daily, which was slowly tapered if patient showed significant clinical improvement. In combination treatment group, the patients were prescribed 50-mg oral minocycline twice daily in combination with 250-mg oral metronidazole thrice daily during the first two weeks and subsequently changed to minocycline monotherapy during the remaining treatment period.

Patients who were prescribed with topical agents such as topical ivermectin, topical metronidazole, and topical calcineurin inhibitors were excluded. All patients received sufficient education and were instructed to avoid possible aggravating or triggering factors. If patient showed significant clinical improvement, oral minocycline treatment was slowly tapered.

Study assessments and treatment outcomes

1) Efficacy assessments

IGA and CEA were assessed by two dermatologists through comparing clinical photographs recorded at baseline and second and third visits. The lower score among those assessed by the two dermatologists was included as a result of this study. Owing to heterogeneity of number and period between patients' visits, IGA 2nd (or CEA 2nd) was defined as the score at the earliest visit before eight weeks of treatment, and IGA 3rd (or CEA 3rd) was defined as the score at the earliest visit during nine to 12 weeks of treatment. Patient's Global Assessment (PaGA) was also recorded at any of the visits between nine and 12 weeks when available. If there was any clinical improvement of erythema, papulopustules, or telangiectasia within two weeks, it was included as an improvement within two weeks in the results.

(1) PaGA ranged from 'excellent' improvement to 'worse'[1-5]. PaGA success was defined as PaGA 'excellent' or 'good' improvement (PaGA 1, 2)[4,16,17].

(2) IGA was assessed on a five-point scale (0: clear, zero papules/pustules; 1: near clear, one or two papules/pustules; 2: mild, three to 10 papules/pustules; 3: moderate, 11~19 papules/

pustules; and 4: severe, >20 papules/pustules)[18]. Clinical improvement in IGA score was defined as a decreased IGA score at least once.

(3) CEA was measured on a five-point scale (0, none; 1, mild; 2, moderate; 3, significant; and 4, severe). CEA success was defined as a decrease of at least one point. Erythema was assessed on five facial regions (forehead, chin, nose, right cheek, and left cheek) and total sum of the erythema scores was up to 20. The sum of scores was calculated to fit a five-point scale, as an average over the five different regions: 0, 0 (none); 1~5, 1 (mild); 6~10, 2 (moderate); 11~15, 3 (significant); and 16~20, 4 (severe)[19].

2) Adverse events

Physicians assessed all adverse events during the treatment of rosacea through electronic medical records.

3) Recurrence

If there was an increase in the score of IGA, CEA, or any clinical aggravation of erythema, papulopustules, or telangiectasia, it was regarded as aggravation of rosacea.

Statistical methods

All statistical tests were performed with IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p<0.05$. Pearson's chi-squared test and Fisher's exact test were used to compare the proportions, and Mann–Whitney U-test and two-tailed t-test were used to compare means.

Maintenance period was measured from the date of discontinuation of systemic treatment to first visit due to aggravation or to last follow-up. The recurrence rate was estimated using Kaplan–Meier method, and difference in the recurrence rates between the two groups was compared using log-rank test.

We estimated odds ratios (OR) and 95% confidence intervals (CI) of risk factors for the recurrence of rosacea in logistic regression analysis[20].

RESULTS

Patient demographic and clinical characteristics

Patient characteristics are shown in Table 1. A total of 58 patients were included. Twenty-nine patients each were in monotherapy group (21 female, 72.4%) and combination group (16 female, 55.1%). In total, nine patients were excluded in IGA, CEA, and PaGA scoring for no photographs or loss-to-follow up (six and three in the monotherapy and combination groups, respectively). The two treatment groups were comparable on demographic and clinical characteristics except age. The median age of monotherapy group (51.8 years) was higher than that of combination group (46.3 years) ($p=0.038$). There was no statistically significant difference in IGA ($p=0.330$) and CEA ($p=0.740$) at baseline. Similar proportions of patients reported positive for scrape (squeezing) test in the treatment groups ($p=0.761$). The most common aggravation factor was sleep deprivation. In monotherapy group 12 patients were erythematotelangiectatic rosacea (ETR) and 15 patients were papulopustular rosacea (PPR) type. In combination group, 11 patients were ETR and 14 patients were PPR type. There were no significant differences in response rate.

Treatment outcomes

Mean follow-up duration was 31.7 weeks. Both groups did not differ in the mean minocycline treatment duration. More patients in combination group showed clinical improvement within two weeks than those in monotherapy group ($p=0.016$) (Table 2). The combination treatment group also reported a significantly lower mean score in IGA 2nd ($p=0.032$), IGA 3rd ($p=0.003$), and CEA 3rd ($p=0.020$). Mean score in PaGA and proportion of PaGA success were comparable between the two groups.

Recurrence rate

Although not statistically significant, combination treatment groups showed longer duration of maintenance period than monotherapy treatment groups (monotherapy, 17.8 weeks and combination therapy, 21.5 weeks, $p=0.835$). Of the 58 patients, 53 (91.4%) reported recurrence of rosacea during the treatment and follow-up period (Table 2).

The Kaplan–Meier curve (Fig. 1) shows recurrence-free survival in the patients. The overall recurrence-free survival analysis (Fig. 1A) revealed no significant difference between the treatment groups ($p=0.160$). Recurrence-free rate of patients at 24 weeks was 33.1% (standard error [SE] 6.3). However, the 24 week-recurrence free rate (Fig. 1B) of monotherapy and combination treatment groups was 18.1% (SE 7.3) and 48.6% (SE 9.6), respectively, which were statistically different ($p=0.042$). The 48 week-recurrence free rate of both groups was similar (monotherapy group: 10.8%, SE 5.9; combination

Table 1. Baseline clinical characteristics of patients

Variable	Monotherapy group (n=29)	Combination group (n=29)	All patients (n=58)	*p*-value
Sex				
Male	8 (27.6)	13 (45.9)	21 (36.3)	0.172
Female	21 (72.4)	16 (55.1)	37 (63.7)	0.172
Mean age (yr)	51.8±9.7	46.3±11.6	49.1±10.9	0.038*
Mean disease duration (wk)	5.9±9.9	4.2±5.0	5.1±7.7	0.431
Baseline IGA (n=total)	2.8±0.9 (n=23)	2.6±0.8 (n=26)		0.330
Baseline CEA (n=total)	1.7±1.3 (n=23)	1.4±1.1 (n=26)		0.740
2nd photograph follow-up (wk)	2.9±1.5	2.4±1.2		0.178
3rd photograph follow-up (wk)	10.7±1.3	10.5±1.4		0.756
KOH positivity (n=total)	19 (70.4) (n=27)	20 (74.1) (n=27)	39 (72.2) (n=54)	0.761
Comorbidity				
Diabetes mellitus	2 (6.9)	3 (10.3)	5 (8.6)	0.640
Hypertension	3 (10.3)	1 (3.4)	4 (6.9)	0.300
Thyroid diseases	1 (3.4)	1 (3.4)	2 (3.4)	>0.999
Brain infarction	1 (3.4)	0 (0)	1 (1.7)	0.313
Uterine myoma	3 (10.3)	1 (3.4)	4 (6.9)	0.300
Hepatitis	1 (3.4)	0 (0)	1 (1.7)	0.313
Gallbladder diseases	0 (0)	1 (3.4)	1 (1.7)	0.313
Ocular diseases	3 (10.3)	0 (0)	3 (5.2)	0.075
Arrhythmia	0 (0)	1 (3.4)	1 (1.7)	0.313
Dyslipidemia	0 (0)	1 (3.4)	1 (1.7)	0.313
Prior therapies				
Prior topical therapies	13 (44.8)	10 (34.5)	23 (39.7)	0.421
Prior systemic therapies	11 (37.9)	9 (31.0)	20 (34.5)	0.581
Prior laser therapies	4 (13.8)	4 (13.8)	8 (13.8)	>0.999
Prior oriental therapies	1 (3.4)	0 (0)	1 (1.7)	0.313
Family history	4 (13.8)	5 (17.2)	9 (15.5)	0.554
Father	1 (3.4)	0 (0)	1 (1.7)	
Mother	2 (6.9)	2 (6.9)	4 (6.9)	
Brother	0 (0)	2 (6.9)	2 (3.4)	
Sister	1 (3.4)	1 (3.4)	2 (3.4)	
Aggravating season				
Summer	10 (34.5)	8 (27.6)	18 (31.0)	0.982
Winter	10 (34.5)	7 (24.1)	17 (29.3)	0.757
Spring or autumn	0 (0)	2 (6.9)	2 (3.4)	0.105
Aggravating factor				
Sunlight	11 (37.9)	12 (41.4)	23 (39.7)	0.788
Sleep deprivation	28 (96.6)	29 (100.0)	57 (98.3)	0.337
Emotional stress	16 (55.2)	15 (51.7)	31 (53.4)	0.792
Drinking alcohol	15 (51.7)	17 (58.6)	32 (55.2)	0.597
Exercise	6 (20.7)	4 (13.8)	10 (17.2)	0.487
Spicy food	14 (48.3)	14 (48.3)	28 (48.3)	>0.999
Sauna	14 (48.3)	15 (51.7)	29 (50.0)	0.793
Cosmetics	7 (24.1)	6 (20.7)	13 (22.4)	0.753

Table 1. Continued

Variable	Monotherapy group (n=29)	Combination group (n=29)	All patients (n=58)	*p*-value
Dye	3 (10.3)	4 (13.8)	7 (12.1)	0.687
Menopause	3 (10.3)	1 (3.4)	4 (6.9)	0.300
Fatigue	3 (10.3)	1 (3.4)	4 (6.9)	0.300
Touching skin	1 (3.4)	2 (6.9)	3 (5.2)	0.553

Values are presented as number (%) or mean±standard deviation. IGA: Investigator's Global Assessment, CEA: Clinician's Erythema Assessment, KOH: potassium-hydroxide. Pearson's chi-squared test and Fisher's exact test were used to compare the proportions; the Mann–Whitney U-test and two-tailed t-tests were used to compare means. *$p<0.05$.

Table 2. Comparison of efficacy outcomes between treatment groups

Variable	Monotherapy group (n=29)	Combination group (n=29)	All patients (n=58)	*p*-value
Mean follow-up duration (wk)	30.2±27.8	33.3±21.0	31.7±24.5	0.286
Mean minocycline treatment duration (wk)	11.8±9.4	12.7±11.4	12.2±10.3	0.755
Improvement within 2 weeks	13 (44.8)	22 (75.9)	35 (60.3)	0.016*
Patients (n)	23	26	49	
IGA 2	2.0±0.9	1.4±0.8		0.032*
IGA 3	1.5±0.9	0.7±0.6		0.003*
CEA 2	1.0±1.0	0.8±0.7		0.441
CEA 3	1.0±0.9	0.5±0.5		0.020*
PaGA	3.9±0.9	4.3±0.7		0.172
PaGA success	16 (69.6)	23 (88.5)		0.157
Maintenance period (wk)	17.8±22.8	21.5±19.4	19.7±21.1	0.835
Overall recurrence rate	28 (96.6)	25 (86.2)	53 (91.4)	0.160
24 week-recurrence free rate, % (SE)	18.1 (7.3)	48.6 (9.6)	33.1 (6.3)	0.042*
48 week-recurrence free rate, % (SE)	10.8 (5.9)	11.1 (6.7)	11.6 (4.5)	0.283

Values are presented as mean±standard deviation or number (%). IGA: Investigator's Global Assessment, CEA: Clinician's Erythema Assessment, PaGA: patient's assessment of treatment result, SE: standard error. Pearson's chi-squared test and Fisher's exact test were used to compare the proportions; the Mann–Whitney U-test and two-tailed t-tests were used to compare means. The recurrence rate was estimated using the Kaplan–Meier method, and differences in the recurrence rates between the two groups were compared using the log-rank test. *$p<0.05$.

treatment group: 11.1%, SE 6.7).

Risk factors of rosacea recurrence within 24 weeks

We performed logistic regression analyses for a treatment group variable and the variables including age, sex, disease duration, family history, and various aggravation factors of patients (Table 1). Logistic regression analyses showed that combination treatment was an important protective factor for the recurrence of rosacea within 24 weeks (OR, 0.223; 95% CI, 0.067~0.747; $p=0.015$) (Table 3). The age, sex, and disease duration were not significant prognostic factors for the recurrence of rosacea within 24 weeks ($p>0.05$). None of the triggering factors were significant prognostic factors for recurrence of rosacea.

Subgroup analysis for scrape (squeezing) test

Of the 54 patients, 39 (72.2%) reported positive results with scrape (squeezing) test (Table 4). In the combination group, the number of patients that clinically improved within two weeks showed significant difference between scrape (squeezing) test positive and scrape (squeezing) test negative groups ($p=0.048$). There was no significant difference in recurrence rate within 24 weeks between the groups, regardless of treatment regimen ($p=0.519$).

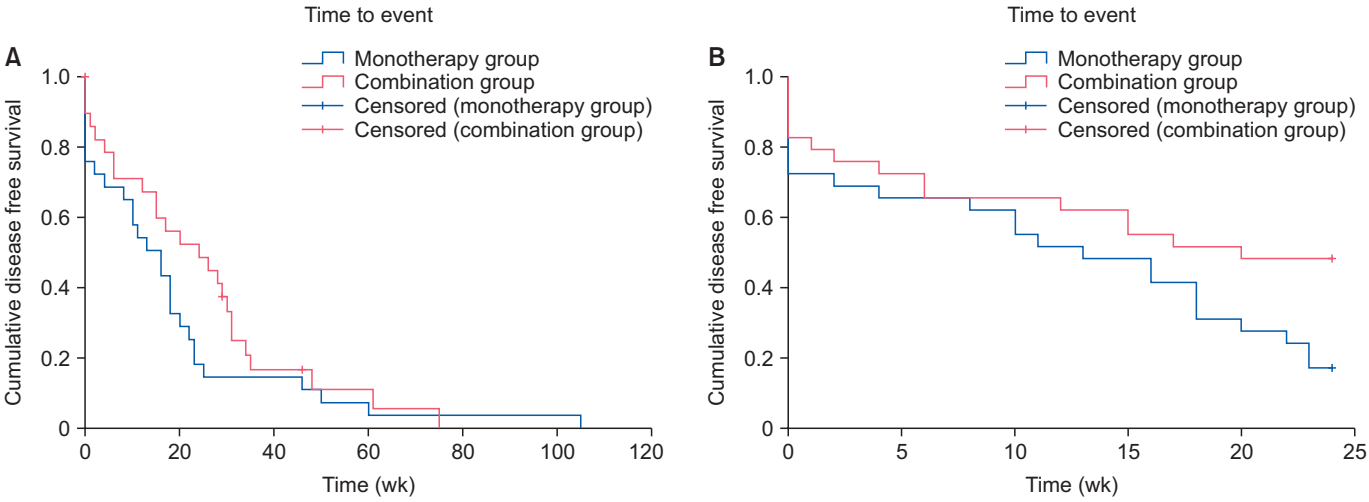

Fig. 1. The Kaplan–Meier curve of the overall (A) and the 24-week (B) recurrence-free survival rate.

Table 3. Odds ratios for recurrence of rosacea within 24 weeks, estimated in logistic regression analyses

Variable	Logistic regression analyses	
	OR (95% CI)	*p*-value
Age	0.922 (0.830~1.024)	0.131
Sex		
Male	Reference	
Female	1.042 (0.334~3.253)	0.688
Disease duration	1.015 (0.878~1.173)	0.182
Treatment		
Minocycline only	Reference	
Minocycline+metronidazole	0.223 (0.067~0.747)	0.015*

OR: odds ratio, CI: confidence interval. *$p<0.05$.

Adverse events

A total of 11 adverse events (Table 5) were reported by 10 patients; three and seven in the monotherapy and combination groups, respectively. There was no significant difference between treatment groups. Gastrointestinal troubles including diarrhea, constipation, and abdominal discomfort were the most common adverse events. Five patients, one in the monotherapy group and four in the combination group, discontinued the oral minocycline treatment because of adverse events, including general edema, angioedema, abdominal discomfort, diarrhea, and urticarial eruption. None of the patients in the combination group discontinued oral metronidazole treatment. There was no severe adverse event noted.

DISCUSSION

Recently, Kubanov et al.[12] reported that *Demodex* mites not only promote the development of acute inflammatory morphological elements, but also increase the duration of rosacea and the probability of recurrence. Oral metronidazole has been suggested as an effective alternative treatment for rosacea due to anti-parasitic activity on *D. folliculorum* and anti-inflammatory effects[5-11]. Pye and Burton reported[8] clinical improvement in papule and pustule counts in 29 rosacea patients after six weeks of oral metronidazole therapy, 200 mg twice daily. In a double-blind, comparative randomized trial of oral metronidazole, 200 mg twice daily, with oxytetracycline, 250 mg twice daily, there was no difference between the two treatment groups at six and 12 weeks, but both drugs showed sustained improvement at 12 weeks[5].

In this study, the combination treatment group showed earlier clinical improvement within two weeks and lower mean IGA and CEA than the monotherapy group. Approximately 48% of patients with combination treatment were disease-free within 24 weeks, higher than that in the oral minocycline group (18.1%, $p=0.042$). Add-on therapy of oral metronidazole appeared to be a significant protective factor for recurrence of rosacea. The overall recurrence rate at 24 weeks was 66.9%, which is comparable with the previous six-month recurrence rate (60%~68%) after treatment with tetracyclines[20-22]. The 24-week recurrence rate of minocycline monotherapy group was 81.9%, which is higher than that reported in previous studies. Han et al.[6] reported that 48.3% of patients, who clini-

Table 4. Subgroup analysis for scrape (squeezing) test using KOH preparation

Variable	Scrape (squeezing) negative group (n=15)	Scrape (squeezing) positive group (n=39)	All patients (n=54)	*p*-value
Improvement in 2 weeks	6 (40.0)	27 (69.2)	33 (61.1)	0.048*
Monotherapy group	3/8 (37.5)	10/19 (52.6)	13/27 (48.1)	0.678
Combination group	3/7 (42.9)	17/20 (85.0)	20/27 (74.1)	0.029*
Recurrence within 24 weeks	11 (73.3)	25 (64.1)	36 (66.6)	0.519
Monotherapy group	6/8 (75.0)	16/19 (84.2)	22/27 (81.4)	0.574
Combination group	5/7 (71.4)	9/20 (45.0)	14/27 (51.8)	0.228

Values are presented as number (%). KOH: potassium hydroxide. *$p<0.05$.

Table 5. Adverse events (AEs)

Variable	Monotherapy group (n=29)	Combination group (n=29)	All patients (n=58)	*p*-value
Number of patients reporting AEs	3 (10.3)	7 (24.1)	10 (17.2)	0.164
Reported AEs	3 (10.3)	8 (27.6)	11 (19.0)	0.094
GI trouble	1 (3.4)	3 (10.3)	4 (6.9)	0.611
Edema	1 (3.4)	2 (6.9)	3 (5.2)	>0.999
Paresthesia	0 (0)	1 (3.4)	1 (1.7)	>0.999
Urticaria	0 (0)	1 (3.4)	1 (1.7)	>0.999
Discolored nail	0 (0)	1 (3.4)	1 (1.7)	>0.999
Blurred vision	1 (3.4)	0 (0)	1 (1.7)	>0.999
Reported AEs per patient				-
0	26 (89.7)	22 (75.9)	48 (82.8)	
1	3 (10.3)	6 (20.7)	9 (15.5)	
2	0 (0)	1 (3.4)	1 (1.7)	
Number of patients with discontinuation	1 (3.4)	4 (13.8)	5 (8.6)	0.352
AEs leading to discontinuation				
GI trouble	1 (3.4)	2 (6.9)	3 (5.2)	>0.999
Edema (general edema, angioedema)	0 (0)	2 (6.9)	2 (3.4)	0.491
Urticaria	0 (0)	1 (3.4)	1 (1.7)	>0.999

Values are presented as number (%). GI trouble: gastrointestinal trouble including diarrhea, constipation, and abdominal discomfort, -: not available.

cally improved after three weeks of metronidazole treatment, were well controlled without recurrence for 20.1 weeks. Mean maintenance duration of combination treatment group was 21.55 weeks, which is similar to that in the previous report.

Of the 54 patients, 39 (72.2%) with scrape (squeezing) test using KOH preparation reported positive results for *Demodex* mites, comparable with the reported frequency of *D. follicu-lorum* in rosacea (35%~90%)[23-25]. Subgroup analysis of scrape (squeezing) test results showed no significant difference in recurrence rate within 24 weeks between scrape (squeezing) test positive and scrape (squeezing) test negative groups, which was contrary to the results of the study by Kubanov et al.[12] In the combination group, more patients of scrape (squeezing) test positive group showed clinical improvement within two weeks than those of scrape (squeezing) test negative group. It implicates that *Demodex* mites are somehow related with the symptom, but considering that it was a qualitative test rather than a quantitative test, it is hard to draw a firm conclusion whether high population yields high disease burden.

Mechanism of metronidazole action in rosacea had been suggested as anti-inflammatory effects by anti-oxidant action through change in neutrophil function and anti-parasitic

activity on *D. folliculorum*[6,7,9-11,13-15]. Han et al.[6] reported that systemic metronidazole was a tolerable and effective option for the treatment of patients with papulopustular rosacea with *Demodex* mites; 74.4% of rosacea patients showed clinical improvement after three weeks of metronidazole treatment, and showed a higher detection rate of *Demodex* mites than patients without any improvement. Studies on oral metronidazole alone for the treatment of *Demodex*-related skin lesions have shown a marked reduction in the inflammatory lesions, but not of the *Demodex* population[26,27]. However, other studies reported clinical improvement with reduction in the mite count after oral metronidazole therapy in *Demodex*-related diseases such as rosacea and demodicidosis[7,13-15]. Hence, it is not clear whether metronidazole directly kills *Demodex* population or inhibits proliferation through various mechanisms.

Based on our results, we speculated that *D. folliculorum* may be attributed to rosacea by leading inflammatory reaction and that the effects of oral metronidazole in early treatment response might be associated with the anti-parasitic activity on *D. folliculorum* mite. Furthermore, mechanism of action of oral metronidazole and minocycline in maintaining remissions of rosacea may involve an anti-inflammatory effect. Since combination treatment group showed significantly earlier and better clinical improvement within 12 weeks than the monotherapy group, oral metronidazole is considered to have a synergistic effect when used in combination with minocycline.

In this study, four patients reported gastrointestinal problems and three reported generalized or local edema during oral minocycline-treated periods. Although one patient in combination group reported mild angioedema on her lips, none of the patients reported previously known severe adverse events of minocycline[28] or metronidazole[29-31], such as serum sickness-like reaction, hypersensitivity syndrome reaction, drug-induced lupus, and seizures. Mild symptoms of central nervous system including dizziness, vertigo, headache, and gastrointestinal effects such as nausea, vomiting, diarrhea, constipation, and abdominal discomforts were most commonly reported with minocycline and metronidazole[4,32,33]. Considering that all adverse events in this study were reported after two-week combined treatment of metronidazole and minocycline, oral metronidazole might have a tolerable safety profile.

Recently, there are concerns regarding antibiotics resistance and consequences of long term antibiotics use. It is recommended to avoid long term use of antibiotics treatment and avoid using monotherapy. Topical therapeutic agents such as topical ivermectin is seem to be a good alternative in order to address this issue[34]. However, there are patients who cannot tolerate topical therapy due to irritation and patients with high disease burden do require systemic therapy. Combination therapy as shown in our study seems to be a good choice in such cases and contribute in reducing antibiotics resistance.

To our knowledge, this is the first study to explore the efficacy of oral metronidazole in reducing relapses in rosacea. There are few limitations to our study. First, due to its retrospective nature, small sample size reduced the statistical power of the study and increased the margin of error. Currently, we are planning a controlled study with large sample size and planning to evaluate whether topical metronidazole is non-inferior to oral metronidazole as an add-on therapy. Second, we did not perform SSSB when evaluating *Demodex* mites. Although SSSB is considered to be the gold standard technique, scrape (squeezing) test using KOH preparation is an effective and practical technique to detect the severity of the condition induced by *Demodex* mite[35]. Third, older patients and those with longer period of disease duration might have been included in the monotherapy group. But there was no statistically significant difference between the treatment groups. Fourth, the exclusion rate of patients in assessment of IGA and CEA scores was 15% of all patients. This causes a smaller sample size in each group and may have biased the results reported in this study.

In conclusion, oral metronidazole can be used for a short-term period with tolerable safety to reach early clinical improvement and to reduce relapses among rosacea patients who are undergoing minocycline treatment. Further large-scale, controlled studies are warranted for evaluation of the efficacy of oral metronidazole in rosacea treatment.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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