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Safety, Efficacy, and Drug Survival of Colchicine in Recurrent Aphthous Stomatitis in a Real-World Setting

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Background: Recurrent aphthous stomatitis (RAS) is a common disorder characterized by episodic ulcerations in the oral mucosa. Although colchicine has been a common systemic treatment for RAS, there is still considerable uncertainty regarding its efficacy and drug survival in this setting.
Objective: We aimed to study drug survival, efficacy, and safety of colchicine for the treatment of RAS, especially in the real clinical setting.
Methods: Between 2012 and 2016, 150 patients given colchicine for RAS were selected for a single-centre retrospective study of real-world efficacy and drug survival.
Results: Among the 114 patients who qualified, 81.6% showed moderate or substantial responses (>25% improvement). Gastrointestinal complications (16.7%), neutropenia (3.5%), and liver enzyme elevation (4.4%) were reported within 2 weeks after initiating treatment. Delayed adverse manifestations were rare. One year after onset, colchicine use was sustained in roughly one-half (49.5%) of patients, whereas many (30.3%) had discontinued the drug, primarily due to lack of efficacy or adverse events. In Cox proportional hazard analysis, minor ulcers were identified as potential determinants of longer drug survival owing to less probability of non-efficacy. However, major ulcers had emerged as predictors of early discontinuation due to lack of efficacy.
Conclusion: In patients with RAS, colchicine may be an effective and safe treatment amenable to long-term maintenance. Monitoring of adverse events within 2 weeks after initiating treatment is advisable to ensure safe administration.

Keywords: Aphthous stomatitis, Colchicine, Drug survival, Efficacy

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a disorder in which well-demarcated, small, and rounded ulcers of oral mucosa develop episodically[1]. It is one of the most common diseases of oral cavity, affecting 5%~25% of the population and typically occurring between 10 and 30 years of age[2,3]. Although multifactorial in aetiology, its pathogenic origins are still largely unknown.

The treatment of RAS remains empiric at present, given a paucity of well-designed trials. Current goals of therapy are to mitigate pain, accelerate mucosal healing, and prevent recurrences, thus greatly improving quality of life. Topical formulations possessing antiseptic, analgesic, and anti-inflammatory properties are recommended for first-line use in susceptible patients. In those refractory to local treatments, short-course systemic glucocorticoid administration or trials of various immunomodulators (such as colchicine) may be attempted. Colchicine suppresses inflammatory pathways by targeting neutrophil chemotaxis and phagocytosis[4,5], showing comparable efficacy but fewer complications than systemic steroids in the treatment of RAS[6]. Unfortunately, past studies have involved small numbers of patients and offer no available data on drug survival or efficacy and safety, especially in routine clinical

practice. Our efforts were centred on actual clinical treatment of RAS, investigating the efficacy, safety, and drug survival of a colchicine regimen.

MATERIALS AND METHODS

This retrospective observational study was undertaken at a single centre in Seoul, Korea after approval by the institutional review board (4-2017-0391). A flowchart of its design is provided in Fig. 1. All patients diagnosed with idiopathic RAS or suspected Behçet's disease (BD) (based on Japanese criteria[7]) between January 2012 and October 2016 were identified via the clinical data repository system. Suspected BD was defined as a combination of RAS and genital ulcers or inflammatory skin conditions (e.g., erythema nodosum), not qualifying as complete or incomplete BD[7]. The list of candidates was then cross-matched with colchicine prescriptions issued in the same time period, narrowing prospective enrolees to those newly treated. Concomitant systemic use of other immune-modulating agents (i.e., steroids, dapsone, thalidomide, or TNF-alpha inhibitors), as shown by medical records, and co-existing systemic conditions, such as sarcoidosis, inflammatory bowel disease, or autoimmune disorders, were grounds for exclusion. The initial regimen for colchicine was 0.6 mg twice a day and was generally used. However, if the patient had mild AE or intolerance issues, the dosage was reduced for purpose of long term use.

We also recorded patient demographic (age, sex) and clinical characteristics, including types of oral ulcers (minor, major, herpetiform) or extraoral BD-related lesions (genital ulcer, papulopustular skin lesion, erythema nodosum, arthritis) and HLA-B51 genotype status, for retrospective analysis.

Patients returning at least two times after treatment onset and taking colchicine for at least 1 month were eligible for therapeutic efficacy assessment. Outcomes were expressed as three- tier estimates of overall improvement in recurrence interval, intensity of pain, and number or duration of oral ulcers as follows: 1) substantial response, >75%; 2) moderate response, 25%~75%; and 3) no response, <25%. All patients taking any dose of colchicine and submitting thereafter to blood testing (complete blood count and routine chemistry) were included in the initial safety analysis. Regular follow-up

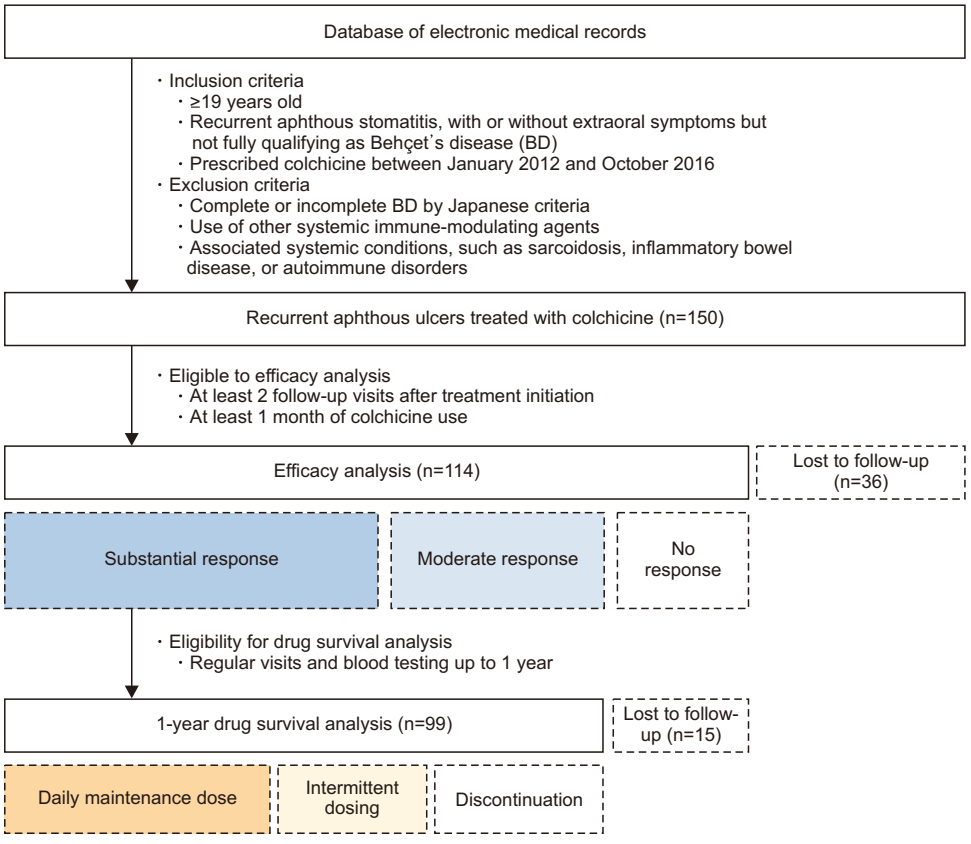

Fig. 1. Flowchart of patient selection and summary of eligible enrolees.

laboratory testing was conducted in patients who continued colchicine treatment. The rate of drug survival, defined as 1-year maintenance of colchicine therapy, was evaluated in long-term follow-up. In event of discontinuation, documented reasons were reviewed. The Cox proportional hazard model was subsequently applied, performing uni- and multivariate analyses of factors potentially influential in withdrawal overall and due to non-efficacy or adverse events (AEs). Predictive analytics software (PASW Statistics ver. 18; IBM Corp., Armonk, NY, USA) powered all computations, setting significance at $p<0.05$.

RESULTS

Electronic medical records were accessed, examining 150 patients diagnosed with RAS and given colchicine between January 2012 and October 2016. Baseline demographics and clinical features are summarized in Table 1. Mean patient age was 48±13.96 years, female accounting for 56.0% (84/150). Most patients (86.0%) presented with minor ulcers only. Although 82 patients (54.7%) exhibited concomitant BD-like extraoral lesions, BD diagnostic criteria were not met during the observation period.

Ultimately, 114 patients (76.0%) qualified for efficacy analysis. Therapeutic responses to colchicine were generally positive, graded as substantial (57/114, 50.0%) or moderate (36/114, 31.6%) (Fig. 1, Table 2).

The same number of patients (114/150, 76.0%) revisited the clinic 2 weeks after initiation of colchicine to assess early safety. At that time, immediate AEs were reported by 26 patients (22.8%), most (n=19) citing gastrointestinal (GI) disturbances (i.e., abdominal pain, diarrhoea, or loose stools). Such complaints were transient in some patients (6/19, 31.6%), improving in others (7/19, 36.8%) after dose reductions (from 1.2 mg/day to 0.3~0.6 mg/day). However, six patients (31.6%) discontinued colchicine as a result.

Mild neutropenia developed in four patients (3.5%), but there were no instances of grade 3 symptomatic neutropenia, as referenced in the Common Terminology Criteria for Adverse Events v5. Neutrophil counts normalized in two of these patients after dose reductions. The other two were forced to abandon colchicine. Five patients (4.4%) also experienced liver enzyme elevations. Three of them fully recovered after dose

Table 1. Baseline characteristics of patients given colchicine for recurrent aphthous stomatitis

Characteristic	Patient (n=150)
Age at presentation (yr)	
Mean (SD)	48 (13.96)
Median (range)	49 (19~81)
Female sex	84 (56.0)
Duration of disease (mo)	
Mean (SD)	119 (119.26)
Median (range)	84 (1~600)
Oral ulcer type	
Minor aphthae only	129 (86.0)
Major aphthae	11 (7.3)
Herpetiform	10 (6.7)
Presentation	
Oral aphthae only	68 (45.3)
Oral lesions and other symptoms of Behçet's disease	82 (54.7)
HLA-B51 genotype	
Positive	50 (33.3)
Negative	100 (66.7)
Treatment prior to colchicine initiation	
Topical agents only	72 (48.0)
Supplements	28 (18.7)
Systemic steroids	50 (33.3)

Values are presented as number (%). SD: standard deviation.

Table 2. Efficacy of colchicine in patients with recurrent aphthous stomatitis and drug survival 1 year after initiating colchicine treatment

Variable	Value
Therapeutic response (n=114)*	
No response	21 (18.4)
Any improvement	93 (81.6)
Moderate response	36 (31.6)
Substantial response	57 (50.0)
Drug survival at 1-year follow-up (n=99)†	
Continuous use	49 (49.5)
Intermittent use	12 (12.1)
Discontinuation	38 (38.4)
Withdrawal due to lack of efficacy	17 (17.2)
Withdrawal due to adverse event	13 (13.1)
Complete remission without recurrence	8 (8.1)

Values are presented as number (%). *Based on recurrence interval, pain intensity, and number/duration of oral ulcers: no response, <25%; moderate response, 25%~75%; substantial response, >75%. †Data on 1-year follow-up in 15 patients was not available for the drug survival analysis.

Table 3. Early adverse events during colchicine treatment of recurrent aphthous stomatitis

Adverse events at initial follow-up visit*	Patient (n=114)
No adverse events	88 (77.2)
GI complaints (abdominal pain, diarrhoea, loose stool)	19 (16.7)
Transient, no dose reduction needed	6 (5.3)
Mild, tolerable after dose reduction	7 (6.1)
Severe, requiring discontinuation	6 (5.3)
Neutropenia	4 (3.5)
Mild, recovery after dose reduction	2 (1.8)
Severe, requiring discontinuation	2 (1.8)
AST/ALT elevation	5 (4.4)
Mild, recovery after dose reduction	3 (2.6)
Severe, requiring discontinuation	2 (1.8)

Values are presented as number (%). GI: gastrointestinal, AST: aspartate aminotransferase, ALT: alanine aminotransferase. *Two weeks after start of colchicine treatment.

reductions, and two ceased treatment (Table 3). During extended follow-up monitoring, another 11 patients experienced various delayed AEs (Table 4), none departing from those mentioned above.

Drug survival for colchicine is shown in Table 2. Long-term data were unavailable for 15 patients who were lost to follow-up. The 1-year overall drug survival rate in those remaining (n=99) was 49.5%, indicating roughly 50% adherence to a colchicine regimen in controlling RAS. Intermittent colchicine dosing also controlled symptoms in 12 patients (12.1%). The drug discontinuation rate was 38.4%. Lack of efficacy (17.2%) was the main reason for discontinuation, followed by AEs (13.1%).

Major ulcers recurred in 7.3% of the 150 enrolees, a proportion aligned with past reports[8-10]. Idiopathic RAS (without concomitant extraoral symptoms) was the sole disorder in 68 patients (45.3%), and HLA-B51 genotype was confirmed in 33.3% (Table 1). A number of significant associations emerged from the univariate Cox proportional hazard model, linking major ulcers to withdrawal fuelled by lack of efficacy (hazard ratio [HR], 4.533; 95% confidence interval [CI], 1.462~14.056) or overall withdrawal of colchicine (HR, 2.944; 95% CI, 1.199~7.230) (Table 5). In addition, idiopathic RAS alone without BD-related symptoms, correlated with overall withdrawal of colchicine (HR, 2.136; 95% CI, 1.000~4.564). However, none of these variables proved significant in the multivariate model. HLA-B51 genotype had no impact on efficacy or drug survival outcomes.

Table 4. Onset of adverse events (AEs) during extended colchicine treatment

Variable	Value (n=114)
Type of AE, day (time to onset of AE)	
GI complaints (abdominal pain, diarrhoea, loose stool)	
Mean (SD)	29.8 (48.2)
Median (range)	7 (3~180)
Neutropenia	
Mean (SD)	33.3 (30.90)
Median (range)	14 (14~84)
AST/ALT elevation	
Mean (SD)	37.5 (39.9)
Median (range)	14 (14~112)
Stratified by time to onset of any AE, no. of patients (%)	
~2 wk	26 (22.8)
>2~4 wk	3 (2.6)
>4~12 wk	4 (3.5)
>12~24 wk	3 (2.6)
>24 wk	1 (0.9)

SD: standard deviation, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

DISCUSSION

In the present study, we systematically analyzed treatment responses, AEs, and long-term usage of colchicine in a sizeable real-world cohort. Overall, 81.6% of patients responded to colchicine, marked by moderate improvement or better. The beneficial effect of colchicine in our RAS cohort was comparable to those of previous studies involving differing ethnicities[11-13]. Based on these observations and data published earlier, roughly one-half of patients with RAS substantially benefit from colchicine monotherapy, another one-third achieving modest therapeutic responses.

In ~22.8% of colchicine users, drug-related AEs were documented during early follow-up, approximately at 2 weeks. Predictably, GI complaints (i.e., abdominal pain, diarrhoea, loose stools) predominated. They were usually dose-dependent and were readily managed by dose reduction or discontinuation. The median interval we observed between drug intake and onset of GI disturbances was 7 days. Because colchicine toxicity may ensue within 24 hours of intake[5], monitoring of acute GI symptoms is advisable upon initiation of treatment.

Drug survival is a surrogate marker of therapeutic efficacy,

Table 5. Uni- and multivariate analyses of factors impacting drug survival

Variable	Overall withdrawal		Withdrawal due to lack of efficacy		Withdrawal due to adverse events	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age	1.138 (0.727~1.781) $p=0.572$	1.037 (0.641~1.677) $p=0.882$	1.152 (0.654~2.029) $p=0.625$	1.106 (0.598~2.043) $p=0.749$	1.171 (0.586~2.339) $p=0.656$	0.931 (0.440~1.970) $p=0.853$
Female†	0.750 (0.432~1.537) $p=0.432$	0.842 (0.397~1.784) $p=0.653$	0.724 (0.279~1.875) $p=0.505$	0.844 (0.312~2.283) $p=0.738$	0.690 (0.232~2.053) $p=0.505$	0.625 (0.192~2.036) $p=0.435$
HLA-B51+‡	0.721 (0.310~1.681) $p=0.449$	0.801(0.3337~1.903) $p=0.615$	0.692 (0.226~2.123) $p=0.520$	0.771 (0.245~2.427) $p=0.656$	0.665 (0.183~2.417) $p=0.536$	0.603 (0.158~2.296) $p=0.458$
Oral ulcer only§	2.136 (1.000~4.564) $p=0.0499$*	1.912 (0.838~4.364) $p=0.124$	2.252 (0.833~6.090) $p=0.110$	1.853 (0.630~5.452) $p=0.262$	2.795 (0.861~9.077) $p=0.087$	2.939 (0.826~10.465) $p=0.096$
Ulcer type‖						
Major	2.944 (1.199~7.230) $p=0.018$*	2.113 (0.728~6.137) $p=0.169$	4.533 (1.462~14.056) $p=0.009$*	3.140 (0.928~10.626) $p=0.066$	4.061 (0.900~18.320) $p=0.068$	2.452 (0.458~13.125) $p=0.295$
Herpetiform	0.687 (0.093~5.087) $p=0.713$	0.628 (0.082~4.805) $p=0.654$	1.133 (0.147~8.716) $p=0.904$	0.915 (0.113~7.443) $p=0.934$	0.046 (0.000~3901.003) $p=0.594$	N/A

Values are presented as hazard ratio (95% confidence interval). N/A: not available. *Statistically significant ($p<0.05$). Reference category: †male; ‡HLA-B51-; §oral ulcer with other symptoms of Behçet's disease, including genital ulcers, papulopustular skin lesions, erythema nodosum, arthralgia, or arthritis; ‖patients with major or herpetiform ulcers.

safety, and practical merit[14]. Overall, 61 of the 99 eligible patients (61.6%) we monitored for up to 1 year seemed satisfied with treatment efficacy. The fact that intermittent dosing was sufficiently efficacious in 12 patients (12.1%) further suggests that colchicine may modify the course of this disease. However, 30 patients (30.3%) were no longer taking colchicine at 1-year follow-up due primarily to non-response or AEs, and 8.1% of patients did not require colchicine after spontaneous complete remission. An overall 1-year drug survival rate of 61.6% may thus be expected for colchicine when managing patients with RAS in daily practice.

Parameters examined as potential confounding factors for drug withdrawal included age, sex, HLA-B51 status, concomitant BD-related symptoms, and ulcer type. In univariate Cox proportional hazard analyses, major ulcers showed significance in predicting withdrawal due to lack of efficacy or overall withdrawal from colchicine. Major oral ulcers signify a more severe clinical form of RAS[8,15] and are often associated with elevated systemic inflammatory markers (IL-6 or IL-8), more so than minor or non-ulcerated (control) counterparts[16,17]. Major ulcers are therefore inherently less responsive to colchicine monotherapy, whereas minor lesions are predictive of therapeutic continuance, responding better to colchicine. This concept is supported by prior reports of lower recurrence rates and fewer, less protracted ulcers in patients with minor (vs. major) forms of RAS[9].

On the other hand, RAS with concomitant extraoral symptoms has shown a significant association with longer drug survival. The therapeutic merit of colchicine in patients with erythema nodosum, arthritis, or genital ulceration has been demonstrated in randomized clinical trials of definitive BD patients, underscoring a certain commonality of treatment responses in both chronic conditions[18,19]. Our cohort also displayed a high prevalence of the HLA-B51 genotype, relative to anticipated levels in Korean populations[20]. It is thus quite possible that other BD symptoms might ultimately appear, fulfilling the diagnostic criteria for BD, although we found no impact on efficacy and drug survival outcomes attributable to this genotype.

Collectively, our data indicate that at least two-thirds of patients with RAS benefitted from colchicine monotherapy, which was continued for up to 1year in roughly one-half of all users. Most AEs or intolerances were encountered very early after drug initiation. Careful monitoring of patients at start of treatment is subsequently recommended to ensure therapeutic

safety in clinical practice.

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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