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**Value of colchicine as treatment for recurrent oral ulcers: a systematic review.**

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## **Abstract**

**Background:** in oral medicine, colchicine is a therapeutic alternative for idiopathic recurrent aphthous stomatitis (RAS), Behçet disease (BD), Periodic Fever, Aphthous stomatitis, Pharyngitis, and cervical Adenitis (PFAPA) syndrome, and Mouth and Genitals Ulcers with Inflamed Cartilage (MAGIC) syndrome. Aim of the present work was to review the literature to evaluate reliability of colchicine against recurrent oral ulcers, either idiopathic, or triggered by an underlying systemic disorder.

**Methods:** A systematic review was conducted, with the following P.I.C.O. (Patient, Intervention, Control, Outcome) question: “In populations with idiopathic or secondary recurrent oral ulcers, is colchicine more effective in improving pain and accelerating healing, compared to other intervention or placebo?”

**Results:** Heterogeneity between RCTs prevented from meta-analysis. Thus, seven RCTs and 3 OCTs were both considered eligible. Four RCTs focused on BD, two RCTs and three OCTs on RAS, and one RCT on PFAPA syndrome. Regarding BD, no significant difference between colchicine and placebo was found in two of three placebo-controlled RCTs, and similar inefficacy was found in one RCT when compared to ciclosporin. One open label RCT showed promising but partial results on colchicine in reducing PFAPA attacks, when compared to corticosteroids. Concerning RAS, colchicine appeared less effective than clofazimine, thalidomide and dapsone, with outcomes similar to placebo and higher gastric discomfort than prednisolone.

**Conclusion:** Role of colchicine as treatment for idiopathic or secondary recurrent oral ulcers is far from being assessed. Further standardized RCTs and crossover trials are needed.

**Keywords:** colchicine, oral ulcers, Behçet disease, systematic review, treatment

## 1 INTRODUCTION

Colchicine is a natural alkaloid derived from two plants of the lily family: *Colchicum autumnale* and *Gloriosa superba*, respectively known as meadow saffron and glory lily.<sup>1</sup>

Due to its anti-inflammatory and anti-mitotic properties, colchicine usage has been expanded in the last decade from FMF and gout to a broader spectrum of cardiovascular, and dermatological conditions.<sup>2-4</sup>

In oral medicine, colchicine is included in the alternative therapeutic option for idiopathic recurrent aphthous stomatitis (RAS), especially when unresponsive to first-line treatments, such as high-potency topical or systemic corticosteroids.<sup>5,6</sup>

Additionally, colchicine might play a role in preventing oral aphthous-like ulcers secondary to peculiar clinical entities, in the form of systemic vasculitis, such as Behçet disease (BD),<sup>7,8</sup> or unusual immune-mediated disorders, such as Periodic Fever, Aphthous stomatitis, Pharyngitis, and cervical Adenitis (PFAPA) syndrome<sup>9,10</sup> and Mouth and Genitals Ulcers with Inflamed Cartilage (MAGIC) syndrome.<sup>11</sup>

Aim of the present work was to carry out a systematic review of the literature on the reliability of colchicine as a treatment for recurrent oral ulcers, either idiopathic, or triggered by an underlying systemic disorder.

## 2 MATERIAL AND METHODS

### 2.1 P.I.C.O. QUESTION

From July 2019 to October 2019, a review of literature was conducted on the use of colchicine on patients with recurrent oral ulcers. The P.I.C.O. (Patient, Intervention, Control, Outcome) question [based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)] for this investigation was: "In populations with idiopathic or secondary recurrent oral ulcers, is colchicine more effective in improving pain and accelerating healing, compared to other intervention or placebo?"

The P.I.C.O. question was then framed as follows:

- Human patients undergoing treatment with colchicine to accelerate healing of idiopathic or secondary recurrent oral ulcers or preventing their occurrence (Patients);
- Each variety of systemic administration of colchicine, as well as any colchicine-based topical formulations for the mouth (Intervention);
- Human patients undergoing no treatment, being administered with no drug, placebo, topic or systemic drugs (Comparison);
- Efficacy of colchicine in terms of relief from symptoms caused by oral ulcers, such as burning, itching, and pain, and effectiveness in accelerating ulcer healing when compared to no drug, placebo, topic or systemic drugs (primary Outcome);

Ability of colchicine to provide a preventive effect, in terms of longer ulcer-free periods when compared to no drug, placebo, topic or systemic interventions (secondary Outcome).

The review was recorded under the PROSPERO registry (registration number CRD42019142599).

### 2.2 SEARCH STRATEGY

No initial restriction has been set concerning date of publication. Inclusion criteria were as follows: RCTs, written in English, conducted on human patients undergoing treatment with any variety of systemic or topic formulation of colchicine to accelerate healing of idiopathic or secondary recurrent oral ulcers or preventing

their occurrence, compared to patients undergoing either no treatment, or placebo, or other topic or systemic drugs.

Exclusion criteria were the following: case reports, case series, observational studies, prospective studies, retrospective studies, reviews; studies not conducted on human patients; papers published in language other than English; "not-inherent" studies, defined as such when:

- Efficacy of colchicine in other fields of medicine was portrayed with no detail on oral ulcers;
- Colchicine was mentioned as a part of a multi-drug approach, even for oral ulcers, so that it is not possible to draw certain conclusions on its standalone efficacy;
- Oral side effects of colchicine treatment were described.

MEDLINE, PubMed Central and other NCBI databases associated with the PubMed platform were searched. The research was also carried out through the following electronic databases: Cochrane Library, NIH (National Institute of Health), Scopus, Web of Science; Up To Date was also scrutinized.

### **3 RESULTS**

The present review acquired 3890 preliminary results, of which 1423 were duplicates. The remaining 2467 studies were scrutinized through a first reading of title and abstract. Due to the aforementioned criteria, 2430 articles were rejected, since 1992 were defined "not inherent", and 438 were published in language other than English.

The remaining 37 articles underwent full reading: of these, 27 papers – 10 case reports, 7 case series, 5 retrospective studies, 2 prospective studies, 2 reviews, 1 case-comparative study - had to be excluded, as well.

Finally, seven RCTs and three OCTs remained. RCTs were scrutinized in order to understand if a meta-analysis could be performed. Due to the heterogeneity of study design, dose and duration of treatment, choice of outcomes and clinical scores between the RCTs, a descriptive approach, inclusive of the evidence coming from the OCTs, was pursued, in contrast with the initial purposes of a pure RCT, meta-analytic-driven review. Figure 1 shows the flow chart of the study selection process. Table 1 shows the number of results obtained from each of the electronic databases scrutinized.

According to these studies, the efficacy of colchicine against oral ulcerations has been experimented among patients affected by BD (Table 2), PFAPA (Table 3), and RAS (Table 4).

### **3.1 SUMMARY OF LITERATURE**

#### **3.1.1 BD**

Four RCTs have tested the efficacy of colchicine against BD, with a concurrent focus on the oral manifestations.

In 1980, Aktulga et al.<sup>12</sup> published the first double blind trial concerning colchicine in BD. From an original sample of 35 patients with BD, 28 patients were randomly assigned and successfully completed a six-month regimen of either colchicine (0.5 mg) or placebo (lactose + phenolphthaleine 60 mg) regimen.

In detail, 14 patients (13 M, 1 F; mean age: 34.2 ± 7.2 years) were administered with three 0.5 mg capsules of colchicine per day, whilst 14 patients (9 M, 5 F; mean age: 33 ± 12.8 years) were given placebo capsules with the same dosage. After the first assessment of signs and symptoms, six monthly visits were performed to elucidate any change in symptoms or signs of BD. Each aspect of BD was considered separately, including

aphthous ulcerations, and compared as “improved”, “no change” or “got worse”. No significant differences were found between colchicine group and placebo group, concerning the severity and recurrence of oral ulcerations ( $p > 0.05$ ).

In 1989, Masuda et al.<sup>13</sup> published a double-blind trial where colchicine was tested against ciclosporin: 96 patients were randomly split into two groups of 49 and 47 patients, with the former undergoing treatment with 1 mg of colchicine per day, and the latter 10 mg/kg of ciclosporin daily, for 16 weeks. Assessment was performed weekly, with a four-grade (0-3) score based on frequency and number of lesions. Ciclosporin group experienced a significant improvement of oral ulcerations when compared to placebo ( $p < 0.001$ ).

In 2001, Yurdakul et al.<sup>14</sup> published a double-blind placebo-controlled trial, in which from an original sample of 116 patients, 84 individuals with BD (45 M, 39 F) were able to complete a 24-month regimen, consisting of either 1-2 mg/day of colchicine or 1-2 mg/day of placebo. Each group included 42 patients, with both treatments consisting of indistinguishable tablets adjusted to body weight. Treatment consisted of 2 tablets daily for patients under 50 Kg, 2-3 tablets daily on alternate days for patients between 50 and 59 Kg, 3 tablets daily for patients weighing 60-75 Kg, up to 3 to 4 tablets daily on alternate days for patients weighing 76-84 Kg, and 4 tablets daily for patients of  $\geq 85$  Kg. With the primary outcome consisting of absence of oral ulceration, and secondary outcome calculated as difference in the mean number of oral lesions, no significant differences were found between colchicine and placebo for both primary and secondary outcome ( $p > 0.05$ ). In 2009, Davatchi et al.<sup>15</sup> enrolled 169 patients with BD in a randomized, double-blind, controlled crossover trial. Patients were randomly assigned to either colchicine (1 mg/day) or placebo for four months, and then switched to the other arm for further four months of treatment.

With a similar dropout rate within the two groups, statistical analysis could be performed based on the data available for 136 patients treated with colchicine and 146 patients administered with placebo. With Iran Behçet Disease Dynamic Activity Measure (IBDDAM) being used, attributing one point for every five oral aphthous lesions, colchicine was significantly more effective than placebo in reducing the IBDDAM score ( $p < 0.05$ ).

### **3.1.2 PFAPA**

In 2016, Butbul et al.<sup>16</sup> published a randomized trial on 18 children affected by PFAPA. After a three-month period when a regular dose of corticosteroids was the only therapy pursued, the sample was randomly split in two groups. A control group I of 10 children continued with no additional therapy, whereas a study group II of 8 children was administered colchicine treatment for three months.

Dose was adjusted in accordance to age, varying from 0.5 to 1.5 mg/day. In this study, no specific information regarding the oral manifestation of PFAPA was provided, since PFAPA attacks were analysed as a whole.

Authors reported that the number of PFAPA attacks in the study group was significantly lower when compared to the baseline ( $p < 0.05$ ) and quasi-significant to control group ( $p < 0.06$ ).

### **3.1.3 RAS**

In 2009, de Abreu et al.<sup>17</sup> published a randomized controlled partially blind study, in which 66 patients with RAS were split in three groups, differentially treated with clofazimine, colchicine and placebo for 60 days and monitored for four months. Interval between the episodes in days, number of lesions, duration in days, diameter in cm, pain, and patient satisfaction were evaluated. With no significant difference at baseline, clofazimine lead to a significantly greater number of patients with no recurrence when compared to other

groups, as well as wider interval between episodes, and a more limited duration of each lesion. Conversely, more than half of colchicine patients interrupted treatment, with 23-45% experiencing gastrointestinal side effects, with 6% of patients giving a high score (8/10 or more) of personal satisfaction.

In 2010, Pakfetrat et al.<sup>18</sup> published a double-blind randomized clinical trial on 34 patients with RAS, equally split in two groups of 17 patients, either treated with 0.5 mg/day of colchicine or with 5 mg of prednisolone for 12 weeks. Diameter and number of lesions, intensity of pain, duration of pain-free intervals, and side effects were scrutinized.

Although both treatments significantly reduced RAS ( $p < 0.001$ ), no significant differences could be detected between the two protocols, in terms of size and number of lesions, recurrence, pain, and length of pain-free intervals. Contrariwise, colchicine lead to a significantly higher occurrence of side effects than prednisolone, with up to 52.9% of patients in the colchicine arm experiencing either gastric disorders, vertigo, or headache. Prednisolone caused hypertension and headache in two patients, respectively.

In 1994, Kats et al.<sup>19</sup> published a four-month open prospective trial, carried out in 20 patients affected by RAS since a mean period of 5.6 years. In the first two months, no drug was administered, and two baseline values, such as number of lesions and pain, through a 0-10 scale, were obtained. In the last two months, patients were given 1.5 mg of colchicine, leading to a significant reduction of both of the aforesaid parameters ( $p < 0.001$ ) and transient mild side effects, such as diarrhoea, nausea, abdominal pain, and urticaria.

In 2003, Altinor et al.<sup>20</sup> published an open placebo-controlled trial whose focus was the effect of colchicine on neutrophil functions in patients affected by RAS. Forty-eight patients were split in two groups and treated with 1.5 mg of colchicine vs 0.5 mg of placebo. With no specifics on the duration of protocol, colchicine was not able to provide a significant reduction of recovery period, similarly to placebo ( $p > 0.05$  in both groups).

In 2009, Mimura et al.<sup>21</sup> published an open, 4 years clinical trial on consecutive 21 patients with severe RAS. Firstly, patients were given systemic prednisone for two weeks, in order to achieve a baseline status. Subsequently, one of the four drugs under scrutiny- colchicine (0.5-1.5 mg/day), dapsone (25-100 mg/day), pentoxifylline (400 mg thrice a day), thalidomide (100 mg/day) – was attributed to each patient, for at least six months. Patients experienced a sudden switch before the six months, whenever side effects occurred. thalidomide proved to be the most effective drug, being “excellent” in 7 of 8 patients, followed by dapsone, being “excellent” in 5 out of 9 cases. Colchicine provided good results, with an “excellent” and “moderate” score experienced in 8 of 10 patients, causing minor gastrointestinal pain and nausea.

#### **4 DISCUSSION**

Based on the findings of the present review, it is not possible to draw solid conclusions regarding the role of colchicine as a reliable treatment for each of BD, RAS and PFAPA, due to the heterogeneity of study designs, posology dose and duration of treatment, choice of outcomes and clinical scores.

Concerning the BD-related studies included in the present review, sample size ranged widely from 28 to 169 patients, as well as duration of treatment varying from 16 weeks to 2 years. Likewise, clinical score varied from a simple choice of primary outcome as “absence of oral ulceration”, to the complex and hard-to-replicate ratio provided in the paper by Aktulga et al.<sup>12</sup>

The placebo-controlled RCTs offered contrasting results, with two of three RCTs showing no significant difference between colchicine and placebo in terms of reduction of number or occurrence of oral lesions. On the other hand, the study with the largest sample but also with the most questionable design, a crossover trial

by Davatchi et al.<sup>15</sup> with no apparent washout period between the two protocols, revealed greater effectiveness of colchicine rather than placebo. Concerning the colchicine vs ciclosporin RCT by Masuda et al.<sup>13</sup> although a similar profile of inefficacy of colchicine against ciclosporin was displayed, some limitations must be pointed out. Firstly, this study provided a generic four grades (0-3) scale used to enumerate frequency and number of oral lesions, with no information provided on the baseline oral status nor if the patients were prevented from the usage of topical measures. Finally, a generic “alleviated” is used to describe the outcome of the protocols. Based on the findings of the present review, it is not possible to draw solid conclusions regarding the role of colchicine as a reliable treatment for BD-related oral ulcers, in line with a Cochrane review on therapies for oral ulcers by Taylor et al.<sup>7</sup> and the latest EULAR recommendations by Leccese et al.<sup>8</sup>, with no meta-analysis available because of heterogeneity of RCTs, biases in the study design, and lack of standardized outcome measures.

The lack of evidence concerning the role of colchicine against oral ulcers caused by PFAPA is even more striking, with just one open label RCT available in literature. In this paper, published by Butbul et al.<sup>16</sup> partial information regarding oral status was provided, with no comparison to oral baseline status, since the primary outcome was then described as the mean of overall PFAPA attacks, together with the disease-free intervals. Such a restricted evidence can be justified by the relatively low frequency and self-limiting nature of PFAPA. Thus, colchicine is usually considered a second-line treatment, when compared to prednisone, in reducing a sudden flare,<sup>10</sup> and to tonsillectomy, with two small RCTs describing valuable effects of surgery in the occurrence and severity of PFAPA flares.<sup>22</sup>

With almost no evidence on PFAPA-related oral aspects, colchicine might exert a prophylactic role against PFAPA, as suggested Butbul et al.<sup>16</sup> In a review published in 2016,<sup>23</sup> a specific role for colchicine was suggested in treating PFAPA unresponsive to tonsillectomy, or PFAPA flares with a predominant oral manifestation, but further evidence is needed to support these claims, as indicated very recently by Gaggiano et al.<sup>9</sup>

Two RCTs and three OCTs discussing the effectiveness of colchicine against RAS were included in this review.<sup>17-21</sup> The conspicuous heterogeneity regarding study design, choice of treatment for comparison (placebo, other drug or no therapy), duration of treatment, spacing from two months to two years, size of sample, ranging from 20 to 66 patients, prevented an evidence-based interpretation of the results. Bearing in mind such discrepancies between the studies, colchicine displayed less effectiveness than clofazimine,<sup>17</sup> as well as thalidomide and dapson,<sup>21</sup> no significant differences from prednisolone<sup>18</sup> or placebo,<sup>20</sup> and a significant objective and subjective improvement only when compared to no therapy.<sup>19</sup>

Furthermore, contrasting evidence emerged regarding the safety profile of colchicine. Of the four RCTs describing side effects, two mentioned significantly higher and more severe side effects in colchicine group, with one<sup>17</sup> reporting an accumulated percentage of 61% of patients forced to interrupt treatment ahead of time, and the other<sup>18</sup> showing 52.9% of the patients under colchicine suffering from gastric disorders, headache and vertigo.

Conversely, Katz et al.<sup>19</sup> illustrated mild and transient side effects in just four of the 20 patients enrolled, although the same dosage - 1.5 mg/day - and duration of treatment - two months – as the two aforesaid trials were deployed. Mild effects were also described in the six months treatment carried out by Mimura et al.<sup>21</sup> where only three of 21 patients were subjected to diarrhoea, which was controlled through small reduction of the 1.5 mg/day of colchicine administered.



No evidence-based guidelines are available regarding which systemic treatment should be considered the first-line for cases of RAS unresponsive to topical measures. A Cochrane review focused on the systemic intervention for RAS<sup>6</sup> collected 25 trials, of which 24 with high or unclear risk of bias, and an inconsistent role attributed to the usage of systemic colchicine. These conclusions are in accordance with the findings of the present review, and those of a previous systematic review on both topical and systemic treatments against RAS.<sup>24</sup>

## **5 CONCLUSION**

Despite being widely used in medicine for centuries, the role of colchicine as a treatment for oral ulcers is yet to be assessed. Further trials are needed, ideally as RCTs adhering to CONSORT statement. Crossover trials are welcomed, especially whenever patients with RAS are to be tested, since this approach is mostly faithful to the everyday clinical approach, where clinicians and patients might go through multiple options. However, in these cases, an appropriate washout period should be included between treatments. Finally, a thorough evaluation of neurological, haematological, nephrological and gastrointestinal repercussions associated with colchicine should be consistently outlined and compared to other therapeutic regimens.

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## **CONFLICT OF INTEREST**

None.

## **ETHICS CONSIDERATIONS**

Given that this is a systematic review, no ethical approval was required.

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<b>ELECTRONIC DATABASE</b>	<b>SEARCH STRATEGY</b>	<b>RESULTS</b>
<b>MEDLINE</b>	“colchicine AND oral disease”	760 results, classified as follows: <ul style="list-style-type: none"> <li>• 1 case-comparative study;</li> <li>• 2 prospective studies;</li> <li>• 2 reviews;</li> <li>• 5 retrospective studies;</li> <li>• 3 OCTs;</li> <li>• 7 RCTs;</li> <li>• 7 case-series;</li> <li>• 9 case-reports;</li> <li>• 165 not-in-English;</li> <li>• 559 not-inherent studies</li> </ul>
	“colchicine AND oral ulcer”	54 results, classified as follows: <ul style="list-style-type: none"> <li>• 52 duplicates</li> <li>• 1 not-inherent study</li> <li>• 1 not-in-English</li> </ul>
<b>Cochrane library</b>	“colchicine AND oral disease”	8 results, classified as follows: <ul style="list-style-type: none"> <li>• 5 duplicates</li> <li>• 3 not-inherent studies</li> </ul>
	“colchicine AND oral ulcer”	3 results, classified as follows: <ul style="list-style-type: none"> <li>• 3 duplicates</li> </ul>
<b>NIH (National Institute of Health)</b>	“colchicine AND oral disease”	11 results, classified as follows: <ul style="list-style-type: none"> <li>• 1 duplicate</li> <li>• 10 not-inherent studies</li> </ul>
	“colchicine AND oral ulcer”	52 results, classified as follows: <ul style="list-style-type: none"> <li>• 1 not-in-English</li> <li>• 15 duplicates</li> <li>• 36 not-inherent studies</li> </ul>
<b>Scopus</b>	“colchicine AND oral disease”	1,738 results, classified as follows: <ul style="list-style-type: none"> <li>• 215 not-in-English</li> <li>• 423 duplicates</li> </ul>

		<ul style="list-style-type: none"> <li>• 1100 not-inherent studies</li> </ul>
	“colchicine AND oral ulcer”	534 results, classified as follows: <ul style="list-style-type: none"> <li>• 11 not-inherent studies</li> <li>• 5 not-in English</li> <li>• 518 duplicates</li> </ul>
<b>Up to date</b>	“colchicine AND oral disease”	147 results, classified as follows: <ul style="list-style-type: none"> <li>• 46 not-in-English</li> <li>• 101 duplicates</li> </ul>
	“colchicine AND oral ulcer”	149 results, classified as follows: <ul style="list-style-type: none"> <li>• 149 not-inherent studies</li> </ul>
<b>Web of Science</b>	“colchicine AND oral disease”	326 results, classified as follows: <ul style="list-style-type: none"> <li>• 1 case report</li> <li>• 5 not-in-English</li> <li>• 118 not-inherent</li> <li>• 202 duplicates</li> </ul>
	“colchicine AND oral ulcer”	108 results, classified as follows: <ul style="list-style-type: none"> <li>• 5 not-inherent studies</li> <li>• 103 duplicates</li> </ul>

**Table 1.** Search strategy and number of results from each of the electronic databases.

**Table 2.** Main characteristics of the eligible studies focused on effectiveness of colchicine against oral ulcerations related to Behçet disease.

<i>Author</i>	<i>Year</i>	<i>Country</i>	<i>Study design</i>	<i>Main features of sample</i>	<i>Colchicine protocol</i>	<i>Placebo/other drug/no therapy protocol</i>	<i>Score/Outcome</i>	<i>Main results</i>
<b>Aktulga et al</b>	1980	Turkey	Double-blind RCT	28 patients  Colchicine arm: 14 patients (13 M, 1 F; mean age: 34.2 ± 7.2 years)  Placebo arm: 14 patients (9 M, 5 F; mean age: 33 ± 12.8 years)	0.5 mg three times a day for six months	Placebo: (lactose + phenolphthalein , 60 mg) three times a day for six months	Ratio:  Denominator = highest score of a sign or symptom – up to a maximum of 3 –multiplied by 6 (number of visits) multiplied by the amount of patients displaying the sign/symptom.  Numerator = add the total score of each patient carrying	No significant difference between colchicine and placebo concerning the severity and recurrence of oral ulcerations (p > 0.05)

							the sign/symptom	
							Evaluation between initial score and mean score of each visit (improved, no change, got worse)	
							Evaluation between initial score and mean score at the last visit (improved, no change, got worse)	
<b>Masuda et al.</b>	1989	Japan	Double-blind RCT	96 patients  Colchicine arm: 49 patients  Cyclosporin : 47 patients  No significant differences in sex/age	1 mg/day for 16 weeks	Other drug: 10 mg/day of Cyclosporin for 16 weeks	Weekly evaluation; score of four grades (0-3) for frequency and number of lesions	Cyclosporin in significantly more effective than colchicine : 33 (70%) of 47 patients under cyclosporin alleviated from oral lesions vs 10 (20%) of 49 patients (p < 0.001)

<b>Yurdakul et al.</b>	2001	Turkey	Double-blind RCT	84 patients  Colchicine group: 42 patients  Placebo groups: 42 patients  45 M; 39 F	1 tablet = 0.5 mg  50-59 Kg: 2 tablets/day  60-75 Kg: 3 tablets/day  76-84 Kg: 3-4 tablets on alternate days  ≥ 85 Kg: 4 tablets/day  Duration of treatment: 24 months	Placebo  1 tablet = 0.5 mg  50-59 Kg: 2 tablets/day  60-75 Kg: 3 tablets/day  76-84 Kg: 3-4 tablets on alternate days  ≥ 85 Kg: 4 tablets/day  Duration of treatment: 24 months	Primary outcome: absence of oral ulceration  Secondary outcome: mean number of oral lesions	No significant differences between colchicine and placebo  P > 0.05 for primary and secondary outcome both in males and females
<b>Davatchi et al.</b>	2009	Iran	Double-blind RCT	169 consecutive patients swapped from colchicine to placebo  Colchicine group: 136 patients  Placebo group: 146 patients	1 mg/day for four months, then swapped to placebo for four months	Placebo: 1 mg/day for four months, then swapped to colchicine for four months	Iran Behçet disease dynamic activity measure (IBDDAM) score  5 oral lesions = 1 point	Colchicine reduced significantly IBDDAM score (2.20 at baseline vs 1.64 after treatment; p = 0.005)  Colchicine significantly more effective than placebo in reducing



IBDDAM score (2.20-1.64 decrease in colchicine group vs 2.11-2.38 in placebo group; p = 0.028)

**Table 3.** Main characteristics of the eligible studies focused on effectiveness of colchicine against oral ulcerations related to Periodic Fever, Aphthous stomatitis, Pharyngitis, and cervical Adenitis syndrome.

<i>Author</i>	<i>Year</i>	<i>Country</i>	<i>Study design</i>	<i>Main features of sample</i>	<i>Colchicine protocol</i>	<i>Placebo/other drug/no therapy protocol</i>	<i>Score/ Outcome</i>	<i>Main results</i>
<b>Butbul et al.</b>	2016	Israel	Open label RCT	18 patients  Control group I: 10 patients (5 M, 5 F; mean age of 6.1 ± 2)  Colchicine group II: 8 patients (6 M, 2 F; mean age of 5.8 ± 2)	Three months of baseline corticosteroids + three months of colchicine  ≤ 5 years old: 0.5 mg/day  5-10 years-old: 1 mg/day  > 10 years old: 1.5 mg/day	No therapy: Three months of baseline corticosteroids + three months with no additional therapy	Number of PFAPA attacks	Colchicine significantly more effective in reducing the attacks than no therapy  Colchicine group: 4.9 ± 2.3 at baseline vs 1.6 ± 1.2 after treatment; p = 0.01  Control group: 2.7 ±

1.5 vs 1.6 ±  
1.2;  
p < 0.06

**Table 4.** Main characteristics of the eligible studies focused on effectiveness of colchicine against oral ulcerations related to idiopathic recurrent aphthous stomatitis.

<i>Author</i>	<i>Year</i>	<i>Country</i>	<i>Study design</i>	<i>Main features of sample</i>	<i>Colchicine protocol</i>	<i>Placebo/ other drug/no therapy protocol</i>	<i>Score/ Outcome</i>	<i>Main results</i>
<b>Kats et al.</b>	1994	Israel	Open, prospective trial	20 patients (10 M, 10 F; mean age: 21.5 ± 1 years)	1.5 mg/day for two months, after two months of no therapy	No therapy for two months before colchicine treatment	Number of lesions; pain (0-10 score) registered once a week	Colchicine reduced number of lesions by 71%, and pain by 77%, when compared to the previous two months with no therapy  Number of lesions declined from a mean of 3.15 ± 0.88 at baseline, to a mean 0.9 ± 0.72 during treatment (p < 0.001)

								Pain decreased from a mean of $7.6 \pm 1.19$ at baseline to a mean of $1.85 \pm 1.73$ during treatment ( $p < 0.001$ )
<b>Altinor et al.</b>	2003	Turkey	Open placebo-controlled trial	48 patients Colchicine group I: 26 patients (14 F, 12 M; mean age: $29.15 \pm 1.91$ years)  Placebo group II: (10 M, 12 F; mean age: $30.73 \pm 1.99$ years)	0.5 mg three times a day  No specifics on duration of protocol	Placebo: 0.5 mg placebo tablets  No specifics on duration of protocol	Recovery period	Colchicine reduced recovery period, although not significantly ( $8.25 \pm 0.23$ days at baseline vs $3.46 \pm 0.28$ days after treatment; $p < 0.1$ )  Placebo group II experienced only a slight reduction ( $8.05 \pm 0.51$ days at baseline vs $7.27 \pm 0.53$ days after treatment; $p > 0.05$ )
<b>De Abreu et al.</b>	2009	Brazil	partially blind RCT	66 patients Colchicine group: 23 patients Clofazimine group:	1.5 mg/day for 60 days	Placebo and other drug  Placebo: two tablets/day for 60 days	Monthly evaluation for six months (2 months of therapy + 4 months of follow-up)	Clofazimine more performing than colchicine  By 4th month: 17-44% disease-free patients under clofazimine vs $\leq 6\%$ disease-free patients under

				23 patients		Clofazimine: 100 mg/day for 30 days followed by 100 mg on alternate days for other 30 days	Interval between the episodes in days (< 7; 7-15; 16-30; > 30)	colchicine/placebo
				Placebo group: 20 group			Number of lesions (1-3; 4-6; > 6)	among patients with no remission: wider intervals, less duration of oral lesions when under clofazimine rather than colchicine/placebo
							Duration in days (1-7; 8-15; > 15)	Colchicine had the highest profile of dissatisfaction: up to 61% discontinued treatment; 23-
							Diameter in cm (0.1-0.5; 0.6-1.0; > 1.0 cm)	45% suffered gastrointestinal side effects
							Pain (mild, moderate, intense)	
							Patient satisfaction (0-10 score)	

<b>Mimura et al.</b>	2009	Brazil	Open clinical trial	Original sample: 27 patients	1 <sup>st</sup> week: 0,5 mg/day	Other drugs	Bi-weekly evaluation	Thalidomide the most performing drug: "excellent" in 7/8 patients
				Final sample:	2 <sup>nd</sup> week: 1 mg/day	Each patient treated with	Drug efficacy classified as:	Good results from colchicine:

21 patients (9 M, 12 F; mean age of 35.5 years)	3 <sup>rd</sup> week-end of treatment: 1.5 mg/day	prednisone for the first 2 weeks  Patients - not enrolled in the colchicine arm - enrolled in one of the following arms:  Dapsone (25 mg/day for the first three days, 50 mg/day for the next three days, 75 mg/day for the next three days, maintenance at 100 mg/day)  Pentoxifylline: 400 mg thrice a day	“excellent”: no relapse  “moderate”: relapse still experienced, with less number and duration of lesions and milder symptoms  “mild”: subjective improvement only  “no response”: no objective/subjective improvement	“excellent”/“moderate” in 8/10 patients  3/10 patients experiences mild side effects from colchicine as transient gastrointestinal pain and nausea  None of the 10 patients under colchicine was forced to interrupt treatment because of side effects
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Thalidomide: 100 mg/day

Duration of each protocol: six months, then switch to each of the remaining arms, so that patients would experience each of the four arms of treatment

<b>Pakfetrat et al.</b>	2010	Iran	Double-blind RCT	34 patients Colchicine group: 17 patients group (8 M, 9 F; mean age: 33.11 ± 11.83 years) Prednisolone	0.5 mg/day for 12 weeks	Other drug Prednisolone: 5 mg/day for 12 weeks	Size and number of lesions, pain, burning sensation, duration of pain-free intervals, side-effects	Both colchicine and prednisolone reduced pain, burning sensation, number of lesions (p < 0.001)  No significant differences between colchicine and prednisolone regarding pain, burning sensation. number and size
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	<p>group: 17 patients (4 M, 13 F; mean age: 29.82 ± 12.09 years)</p>	<p>of lesions, duration of pain-free intervals ( p &gt; 0,05)</p> <p>Side effects significantly higher in the colchicine group (52.9% vs 11.8%; p 0.027), mostly as gastric disorders</p>
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**Figure 1.** Flow-chart of review synthesis.



