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A Double-Blind Trial of Colchicine in Behçet's Syndrome

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Objective. **Colchicine is a widely used treatment for Behçet's syndrome, even though in a previous 6-month controlled study, it was shown to be effective only in controlling erythema nodosum and arthralgias. We reassessed the effect of colchicine in Behçet's syndrome in a study conducted among a larger group of patients for 2 years.**

Methods. **We randomized 116 patients with Behçet's syndrome (60 male/56 female), who had active mucocutaneous disease without eye or major organ involvement, to receive either placebo or colchicine (1–2 mg/day, adjusted to body weight) in a double-blind trial for 2 years. The primary outcome measure was the sustained absence of any lesions during treatment (complete response). The secondary outcome measure was the difference in the number of mucocutaneous lesions or arthritic joints between the active drug and placebo arms. Women and men were analyzed separately.**

Results. **Eighty-four patients (72%; 45 male, 39 female) completed the 24-month study. Kaplan-Meier analyses showed significantly more complete responses in the colchicine treatment group in terms of reduced occurrence of genital ulcers ($P = 0.004$), erythema nodosum ($P = 0.004$), and arthritis ($P = 0.033$) among the women, and reduced occurrence of arthritis ($P = 0.012$) among the men. The mean numbers of genital ulcers ($P = 0.001$), erythema nodosum lesions ($P = 0.002$), and arthritic joints ($P = 0.014$) among the women were less in the colchicine group, and the mean number of arthritic joints ($P = 0.026$) among the men was less in the colchicine group. Adverse effects were similar in both groups.**

Conclusion. **Colchicine may be useful for treating some of the manifestations of Behçet's syndrome, especially among women. This might be a reflection of less severe disease among the women.**

Behçet's syndrome is a systemic vasculitis of unknown etiology that is found in small and large vessels and characterized by variable clinical features. Almost all patients have recurrent oral ulceration, followed in frequency by genital ulcers, a variety of skin lesions, arthritis, panuveitis, thrombophlebitis, gastrointestinal disease, and central nervous system involvement (1).

Colchicine is widely used in Behçet's syndrome. The evidence for its efficacy is based mainly on open studies (2–4). It is claimed that colchicine exerts its beneficial effect through inhibition of leukocyte chemotaxis. However, the evidence for this increase in chemotaxis is, at best, debatable (2–5). We had previously shown that colchicine was effective in Behçet's syndrome only in controlling erythema nodosum and arthralgias. That study, conducted several years ago, was a double-blind, placebo-controlled, 6-month study conducted among 35 patients (6). In the present study, we assessed the effectiveness of colchicine in a 2-year randomized, double-blind, placebo-controlled study among a larger group of patients of both sexes. The randomization and all analyses were done separately for each sex, because men are known to have distinctly more severe disease compared with women (7,8).

PATIENTS AND METHODS

Patients. The multidisciplinary Behçet's Syndrome Research Center at the Cerrahpaşa Medical School, established 25 years ago, has more than 4,000 registered patients and meets weekly. Consecutive patients attending the center were recruited into the study between November 1991 and Decem-

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ber 1995. The recruitment period was 24 months. All patients fulfilled the criteria for the diagnosis of Behçet's syndrome (9).

Inclusion criteria. All patients were required to meet the inclusion criteria, which meant that they had to 1) be consecutive patients (male or female), 2) be 18–35 years of age, 3) have active disease, 4) have a disease duration of ≤2 years, and 5) live at a reasonable traveling distance from our center. Active disease was defined as the minimum presence of oral or genital ulceration or erythema nodosum occurring at least 3 times within the preceding 6 months. The disease duration was defined as the time that had elapsed since the diagnostic criteria had been fulfilled.

Exclusion criteria. We excluded patients who 1) had received immunosuppressive agents, steroids, or colchicine within the preceding 6 months, 2) had organ involvement requiring immunosuppression, or 3) had eye disease, especially with retinal involvement, during the recruitment period. However, patients who had only a few cells in vitreous body were included if their visual acuity was >9/10 (assessed on a 10-line scale, with a best vision of 10/10).

Patients were to be withdrawn from the study in the event of a major systemic or life-threatening manifestation such as severe eye, major vein, or central nervous system involvement. Women were strictly advised to take appropriate contraceptive measures. The study was performed according to the principles of the Declaration of Helsinki. The patients gave their written informed consent after a detailed explanation about the aims of the study.

Randomization. Among the patients fulfilling the entry criteria, only those who gave their written informed consent were included in the randomization. The randomization was done separately for each sex. In each sex group, equal numbers of cards that were assigned to either the active drug or the placebo arm were mixed, drawn, and placed sequentially on a list by a secretary not involved in running the trial. The code was kept in a sealed envelope by one of the authors (HY) and was opened only after all data had been entered into the computer for analysis. The allocation to the study and the dispensing of the medications were done by a research assistant.

Patients for the study were all screened and recruited by the same rheumatologist (SY). At each visit, the patients received a bottle containing either 0.5 mg colchicine or placebo tablets that were identical to the active drug in appearance and taste. Doses were adjusted to body weight: patients who weighed <50 kg took 2 tablets daily, those weighing 50–59 kg took 2 tablets and 3 tablets on alternate days, those weighing 60–75 kg took 3 tablets daily, those weighing 76–84 kg took 3 tablets and 4 tablets on alternate days, and patients weighing ≥85 kg took 4 tablets.

The patients received the assigned study medication until any of the following occurred: 1) emergence of a major systemic or life-threatening manifestation of the disease such as severe eye involvement, major vein, or central nervous system involvement requiring immunosuppressive agents; 2) noncompliance with the study medication; 3) pregnancy; or 4) any other requests for withdrawal. Unused pills were collected and counted for compliance at each visit and the compliance rates were expressed as the percentage of pills used in each arm of the study groups. The patients were permitted to use local treatment for oral and genital ulceration and acetaminophen or nonsteroidal antiinflammatory drugs for joint disease, if needed.

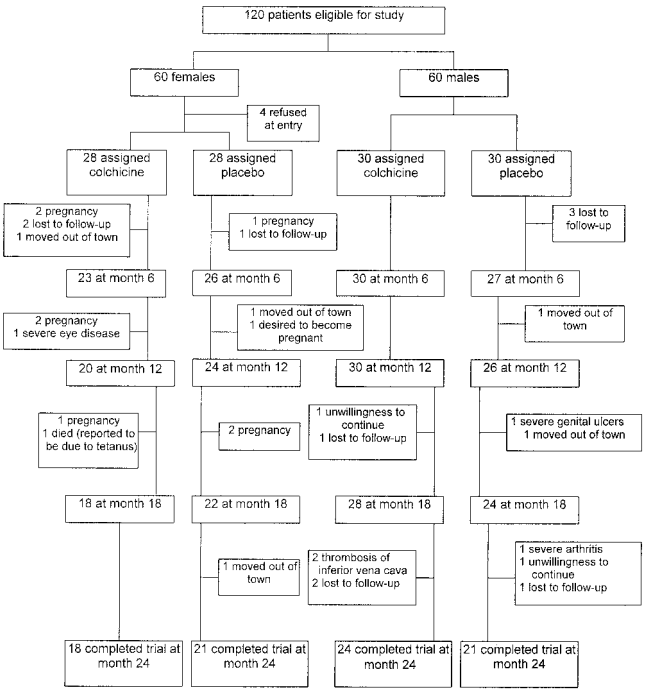

Figure 1. Outcome of treatment randomization and followup of patients with Behçet's syndrome.

Followup and data collection. The patients were seen monthly by a rheumatologist (SY), as well as a dermatologist (CM). The number of oral and genital ulcers, episodes of erythema nodosum, and joints with arthritis was recorded at each visit. The number of follicular lesions was graded as 0 = no lesions, 1 = 1–5 lesions, 2 = 6–15 lesions, and 3 = >15 lesions. A detailed ophthalmologic examination, including a slit lamp examination and tri-mirror fundus-lens ophthalmoscopy, was done every 3 months and whenever needed.

All participating physicians were blinded to the patients' allocation to the study arms. Adverse effects were recorded by questioning patients regarding loss of appetite, nausea, abdominal pain, and diarrhea or any other symptom volunteered by the patient at each visit.

Outcome measures. The effects of colchicine or placebo on each lesion were analyzed separately. For the data analysis, we chose the complete absence of oral ulceration, genital ulcers, erythema nodosum, follicular lesions, and arthritis during the entire study period as the primary outcome measure related to that particular lesion. Our secondary outcome was the differences in the mean number of mucocutaneous lesions or joints with arthritis between the patients in the colchicine arm and the placebo arm. Male and female groups were analyzed separately.

Statistical analysis. Comparisons of the baseline demographic data were made by Student's *t*-tests and chi-square tests (both 2-tailed). All analyses were done by the intent-to-treat principle. Thus, patients who had attended the clinic at

Table 1. Patient characteristics at baseline

	Females (n = 56)		Males (n = 60)	
	Colchicine (n = 28)	Placebo (n = 28)	Colchicine (n = 30)	Placebo (n = 30)
Mean ± SD age, years	26.7 ± 4.8	27.2 ± 5.5	27 ± 5.5	27.3 ± 5.3
Mean ± SD body weight, kg	60.1 ± 10.3	58.3 ± 10.1	69.7 ± 10.8	69.8 ± 13.7
Mean ± SD disease duration, months	8 ± 8.8	6.8 ± 6.8	8.2 ± 8.4	10.3 ± 8.3
Clinical manifestations, no. (%) patients				
Oral ulceration	28 (100)	28 (100)	30 (100)	30 (100)
Genital ulcers	24 (86)	23 (82)	28 (93)	24 (80)
Folliculitis	19 (68)	20 (71)	27 (90)	25 (83)
Erythema nodosum	18 (64)	16 (57)	14 (47)	15 (50)
Arthritis	4 (14)	7 (25)	7 (23)	13 (43)
Positive pathergy result	24 (86)	24 (86)	24 (80)	23 (77)
HLA–B5 positive, no. (%) patients	16/21 (76)*	12/25 (48)*	14/22 (64)	9/19 (47)
Treatment received in the past, no. (%) patients†	3 (11)	1 (4)	1 (3)	4 (13)

* $P = 0.051$.
† All patients had previously received colchicine and 1 patient had received, in addition, cyclophosphamide.

least once after the beginning of treatment were analyzed for the outcome measures. All outcome measures were based on the data obtained by the physicians at monthly clinic visits. The lesions that might have occurred and healed between the visits were disregarded.

Kaplan-Meier plots were developed for the time-dependent distribution of the primary outcome measures of different manifestations. Time 0 was the beginning of treatment (month 0), at which point all patients were considered responders. Data were compared between the 2 study arms with log-rank tests.

For our secondary outcome measure analysis, the Mann-Whitney U test (2-tailed) was used. In these calculations, the data were derived from the total number of mucocutaneous lesions or arthritic joints in each patient during the whole trial, irrespective of the length of time he/she remained in the trial. Data were expressed as the mean and SD.

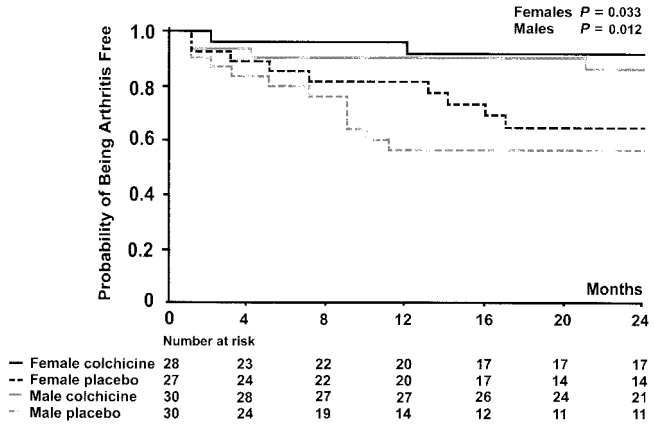

Figure 2. Distribution of time to first occurrence of sustained absence of arthritis. All outcome measures were based on the data obtained by the physicians at monthly clinic visits.

RESULTS

Study population. One hundred twenty consecutive patients were eligible for the study. Four women declined to participate. Eighty-four patients (72%; 45 male, 39 female) completed the 24-month study (Figure 1). There were no significant clinical differences at baseline (Table 1), except that HLA–B5 was significantly more frequent ($P = 0.051$) in the colchicine arm compared with the placebo arm among the female patients.

One hundred patients (86%) were new. Sixteen patients were already being followed up at our outpatient clinic, of whom 9 had previously received colchicine treatment. One patient had previously received cyclophosphamide. None of these patients had received these medications during the 6 months preceding their entry into the study, which is consistent with our exclusion criteria. There were no differences in the number of dropouts or reasons for withdrawal (Figure 1) between the 2 treatment arms. This was true for either sex. One woman among the placebo arm was excluded from the outcome analyses because she did not return to the clinic after the randomization.

Compliance rates, as calculated from the returned pill counts, were 91% among the women receiving colchicine, 95% among the women receiving placebo, 91% among the men receiving colchicine, and 92% among the men receiving placebo.

Arthritis. *Primary outcome.* Colchicine favorably suppressed the emergence of new attacks of arthritis, both among the women and among the men (Figure 2). At the end of the trial, 91% of the female patients in the colchicine arm remained arthritis free as compared with

Table 2. Mean number of mucocutaneous lesions and arthritic joints in each study arm*

Outcome	Females			Males		
	Colchicine (n = 28)	Placebo (n = 27)	P†	Colchicine (n = 30)	Placebo (n = 30)	P†
Oral ulceration	15.6 ± 12.3 (0–40)	21.3 ± 13.6 (2–56)	0.136	25.7 ± 14.0 (5–51)	24.9 ± 19.7 (2–88)	0.492
Genital ulcers	0.1 ± 0.5 (0–2)	2.6 ± 4.6 (0–16)	0.001	2.4 ± 4.3 (0–20)	3.5 ± 7.2 (0–38)	0.994
Erythema nodosum	1.4 ± 3.9 (0–17)	6.0 ± 14.9 (0–71)	0.002	0.7 ± 1.5 (0–6)	2.0 ± 6.6 (0–36)	0.203
Arthritic joints	0.3 ± 1.1 (0–6)	2.4 ± 6.0 (0–29)	0.014	2.8 ± 11.0 (0–56)	4.4 ± 7.9 (0–31)	0.026
Folliculitis	4.1 ± 3.5 (0–12)	5.9 ± 5.2 (0–18)	0.290	15.7 ± 8.5 (3–34)	13.1 ± 8.3 (1–31)	0.190

* Values are the mean ± SD (range) unadjusted total number of mucocutaneous lesions or arthritic joints in patients during the whole trial, irrespective of the length of time he/she remained in the trial. All outcome measures were based on the data obtained by the physicians at monthly clinic visits.
† Mann-Whitney U test (2-tailed).

64% in the placebo arm ($\chi^2 = 4.55$, $P = 0.033$ by log-rank test). The corresponding values for the men were 86% and 56% among the colchicine and placebo arms, respectively ($\chi^2 = 6.31$, $P = 0.012$ by log-rank test).

Secondary outcome. The mean (±SD) number of inflamed joints was also significantly less in the colchicine arm compared with the placebo arm, both among the women (0.3 ± 1.1 versus 2.4 ± 6.0, respectively; Mann-Whitney U = 276.5, $P = 0.014$) and among the men (2.8 ± 11.0 versus 4.4 ± 7.9, respectively; Mann-Whitney U = 332.5, $P = 0.026$) (Table 2).

Erythema nodosum. *Primary outcome.* There were significantly fewer new attacks of erythema nodosum among the female patients in the colchicine arm compared with those in the placebo arm (Figure 3). At the end of the trial, 79% of the female patients in the colchicine arm remained erythema nodosum free as compared with 39% of the female patients in the placebo arm ($\chi^2 = 8.10$, $P = 0.004$ by log-rank test). Among the male patients, the corresponding values were 76% and 60% among the colchicine and placebo arms, respectively ($\chi^2 = 3.30$, $P = 0.069$ by log-rank test).

Secondary outcome. The mean (±SD) number of erythema nodosum lesions was significantly less in the colchicine arm compared with the placebo arm among the women (1.4 ± 3.9 versus 6.0 ± 14.9, respectively; Mann-Whitney U = 217.5, $P = 0.002$) but not among the men (0.7 ± 1.5 versus 2.0 ± 6.6, respectively; Mann-Whitney U = 382, $P = 0.203$) (Table 2).

Genital ulcers. *Primary outcome*. There were significantly fewer new attacks of genital ulceration among the female patients in the colchicine arm compared with those in the placebo arm (Figure 4). At the end of the trial, 89% of the female patients in the colchicine arm remained genital ulceration free as com-

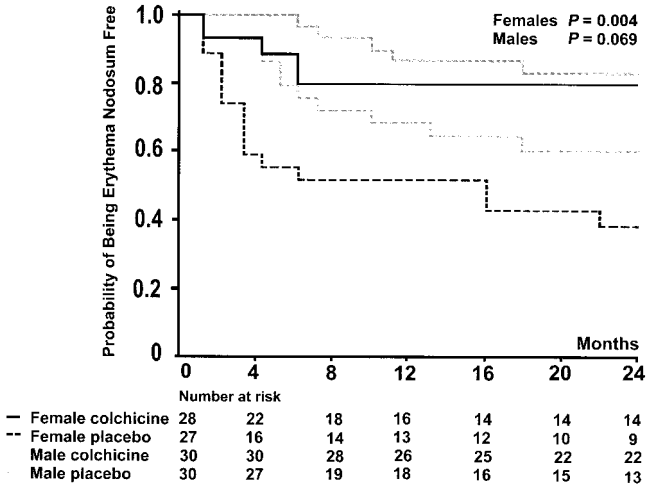

Figure 3. Distribution of time to first occurrence of sustained absence of erythema nodosum. All outcome measures were based on the data obtained by the physicians at monthly clinic visits.

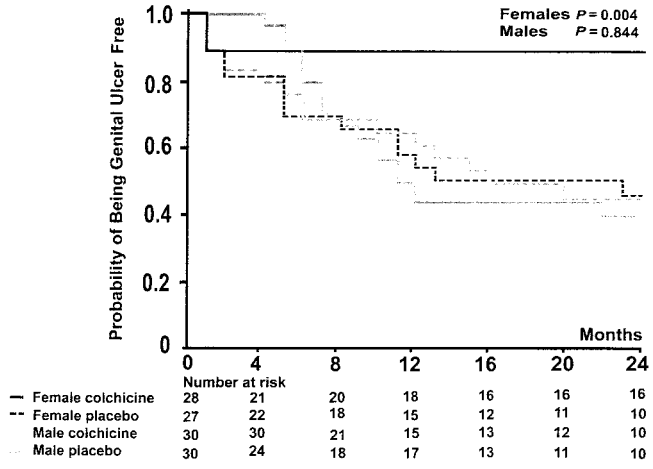

Figure 4. Distribution of time to first occurrence of sustained absence of genital ulcers. All outcome measures were based on the data obtained by the physicians at monthly clinic visits.

pared with 46% of the female patients in the placebo arm ($\chi^2 = 8.27$, $P = 0.004$ by log-rank test). No such difference was observed among the male patients receiving either colchicine or placebo.

Secondary outcome. The mean (±SD) number of genital ulcers was also less in the colchicine arm compared with the placebo arm among the female patients (0.1 ± 0.5 versus 2.6 ± 4.6, respectively; Mann-Whitney U = 212.5, $P = 0.001$). Among the male patients, the number of genital lesions was similar in each treatment arm (colchicine 2.4 ± 4.3 versus placebo 3.5 ± 7.2; Mann-Whitney U = 449.5, $P = 0.994$) (Table 2).

Oral ulceration. *Primary outcome.* No significant differences in the occurrence of oral ulceration were found between the colchicine and placebo arms in either sex (women $\chi^2 = 1.14$, $P = 0.286$ and men $\chi^2 = 0.93$, $P = 0.334$ by log-rank test) (Figure 5). Almost all patients had oral aphthae within the first 4 months of the study.

Secondary outcome. There were also no significant differences in the mean (±SD) number of oral lesions between the colchicine and placebo arms in either the female patients (15.6 ± 12.3 versus 21.3 ± 13.6, respectively; Mann-Whitney U = 298.5, $P = 0.136$) or the male patients (25.7 ± 14.0 versus 24.9 ± 19.7, respectively; Mann-Whitney U = 403.5, $P = 0.492$) (Table 2).

Folliculitis. *Primary outcome.* No differences in the occurrence of folliculitis were observed between the colchicine and placebo arms in either sex (women $\chi^2 = 1.64$, $P = 0.201$ and men $\chi^2 = 0.08$, $P = 0.779$ by log-rank test) (Figure 6).

Secondary outcome. The mean (±SD) number of follicular lesions was also similar between treatment arms among the women (colchicine 4.1 ± 3.5 versus placebo 5.9 ± 5.2; Mann-Whitney U = 315.5, $P = 0.290$) as well as the men (colchicine 15.7 ± 8.5 versus placebo 13.1 ± 8.3; Mann-Whitney U = 361.5, $P = 0.190$) (Table 2).

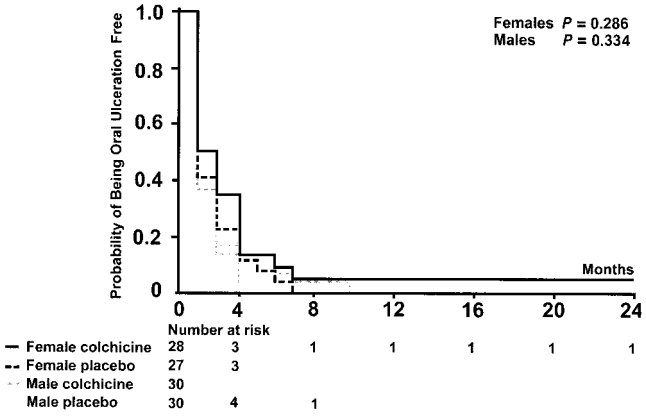

Figure 5. Distribution of time to first occurrence of sustained absence of oral ulceration. All outcome measures were based on the data obtained by the physicians at monthly clinic visits.

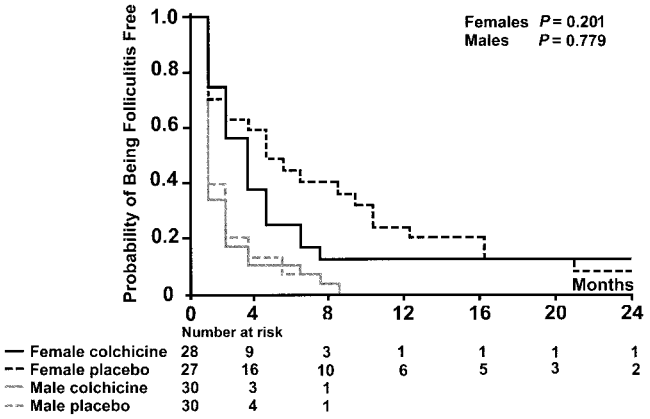

Figure 6. Distribution of time to first occurrence of sustained absence of folliculitis. All outcome measures were based on the data obtained by the physicians at monthly clinic visits.

Other symptoms and additional treatment. There was 1 male patient from the colchicine arm who had several attacks of bilateral anterior uveitis without any decrease in vision. Thrombophlebitis developed in 8 patients, all men, during the trial; this was manifested as superficial thrombophlebitis in 5 patients from the placebo group and in 1 patient from the colchicine group. These events did not necessitate withdrawal from the study. However, in the colchicine arm, inferior vena caval thrombosis developed in 2 patients, and these 2 patients had to be withdrawn from the trial (Figure 1). In a small number of patients, additional treatment had to be given. This is outlined in Table 3.

Adverse effects. The adverse effects observed at each visit were quite similar in each treatment arm, as summarized in Table 4. These events were mild, necessitating dose reduction of the assigned medications in only a few patients. Most patients returned to the usual dosage after the dose adjustments.

DISCUSSION

This 2-year placebo-controlled study showed that colchicine has different degrees of effect on the different manifestations of Behçet's syndrome. Furthermore, its efficacy was not the same between the male and the female patients. Colchicine was clearly effective for arthritis in both sexes. Statistically significant beneficial

Table 3. Additional treatment*

Sex	Type of additional treatment (no. of patients)	
	Colchicine	Placebo
Female	NA	3 pulses of 1 gm methylprednisolone for genital ulcers at the fourth month, then 100 mg thalidomide for 1 week and 50 mg for 3 weeks (n = 1).
Male	Short courses of NSAIDs, mainly ibuprofen for arthritis (n = 3); local steroid for arthritis (n = 1).	Short courses of NSAIDs, mainly ibuprofen for arthritis (n = 3); local steroids for arthritis (n = 3); a short course of steroids for local myositis (n = 1); a short course of steroids for intracranial hypertension at month 12 (n = 1).

* NA = no additional treatment; NSAIDs = nonsteroidal antiinflammatory drugs.

effects of colchicine on erythema nodosum and the genital lesions were seen only among the women.

By chance, a significantly greater number of patients who were HLA–B5 positive were randomized to receive colchicine among the women. We also did formal analyses (data not given) among the HLA–B5–positive patients only, evaluating both of our outcome measures. In the majority of these patients, the same effects of colchicine persisted. Thus, we do not believe that the HLA status had much to do with the observed responses to this medication.

For genital ulcers, colchicine had a marked beneficial effect among the female patients, and this was observed both in the primary and in the secondary outcome measures. In contrast to the pronounced effect of colchicine on genital ulcers in women, there was no clear-cut effect of colchicine on oral ulceration in either sex. Even though the mean number of oral lesions among the women receiving colchicine was less than the number of oral lesions in those receiving placebo, this was not statistically significant. It is possible that the number of female patients studied was not enough to show a real difference in response (a beta error); however, there was also no difference in primary outcomes for oral ulceration in either sex. A similar beta error might also have been operative in our interpretation of the primary outcome measure for erythema nodosum among the male patients.

It is known that Behçet's syndrome runs a more severe disease course among male patients and in patients with a younger age at onset. Since the patients in this study were relatively young and had a short disease duration at entry to the study, one could postulate that our study design could have underestimated the efficacy of colchicine. On the other hand, one should also consider the fact that the patients studied in this trial had limited disease and our results would not be applicable to those with extended disease. In the presence of more potent drugs, such as azathioprine or cyclosporin A (10,11), the current use of colchicine is mainly restricted to those patients who develop mild mucocutaneous lesions. Finally, considering the geographic variability in disease expression of Behçet's syndrome, the results obtained with colchicine might not apply to the sporadic cases seen in the US and other Western countries, in which the genetic background and disease expression differ from those in the endemic areas such as that reported in this study (12). On the basis of the present study, no conclusion can be made in terms of the effect of colchicine on the more serious manifestations of the disease. Most probably due to our patient selection process, these lesions were seldom observed in both groups and arms of the trial.

In this study, the randomization and allocation of the patients into the study groups and the data analyses were done separately for each sex because we had shown

Table 4. Adverse effects*

Adverse effects	Females				Males			
	Colchicine (n = 19)		Placebo (n = 22)		Colchicine (n = 20)		Placebo (n = 22)	
	≤2 visits	≥3 visits	≤2 visits	≥3 visits	≤2 visits	≥3 visits	≤2 visits	≥3 visits
Loss of appetite	5	3	10	3	10	2	5	7
Nausea	4	7	11	7	6	2	6	3
Abdominal pain	10	4	7	3	6	3	5	8
Diarrhea	9	2	7	0	8	3	9	3

* Values are the number of patients who responded with positive answers to a predefined list of questions regarding adverse events.

earlier that men distinctly had a more severe disease course, in terms of both morbidity and mortality (7,8). The preferential efficacy of colchicine among the female patients is interesting. It might simply reflect the less severe disease expression among the women. It might also indicate a true sex difference in response to colchicine; however, we could not come across any previous reports of this.

In conclusion, colchicine is useful for treating the arthritis and some of the mucocutaneous manifestations of Behçet's syndrome. Female patients, for reasons yet to be explained, seem to respond better to this medication. Based on the results from the current study, we recommend limiting the use of colchicine to the treatment of arthritis in either sex and to the treatment of erythema nodosum and genital lesions seen mainly among the female patients.

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