Colchicine in Behçet Syndrome: A Longterm Survey of Patients in a Controlled Trial

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ABSTRACT. ***Objective.*** To test the hypothesis that colchicine use during early disease decreases immunosuppressive use in Behçet syndrome (BS) in the long term.

Methods. Patients with BS who participated in a double-blind, placebo-controlled trial of colchicine 16.6 ± 1.1 years ago were evaluated for immunosuppressive use during the posttrial period.

Results. We could contact 90/116 patients; 28 (31%) received immunosuppressives during the posttrial period, 14 being from the colchicine arm. Posttrial colchicine use and cumulative duration were similar between patients who received immunosuppressives and those who did not.

Conclusion. Continuous use of colchicine, even when initiated at an early disease stage, does not seem to decrease the use of immunosuppressives in the long term. (J Rheumatol First Release Feb 15 2014; doi:10.3899/jrheum.130847)

Key Indexing Terms:
BEHÇET SYNDROME COLCHICINE PROGNOSIS

Behçet's syndrome (BS) may involve many organ systems, leading to increased disability and mortality in a substantial proportion of patients over time[1]. The activity is highest during the initial years and tends to decrease with time[2]. With the exception of major vessel disease and central nervous system (CNS) involvement, most complications of BS occur during the initial years of the disease course[1]. Being male, and a young age at disease onset, are the only well-established prognostic factors associated with a poor outcome[3].

Treatment of BS is based largely on the suppression of existing symptoms, with the aim to prevent subsequent organ damage[4]. Colchicine, an alkaloid-inhibiting leukocyte function once considered a panacea for almost all manifestations of BS (while largely having been replaced by immunosuppressives[5,6]), is still prescribed by many physicians for a wide range of manifestations. On the other hand, randomized controlled trials of colchicine had shown a modest effect for this drug in the management of mucocutaneous manifestations and arthritis of BS[7,8,9]. Accordingly, colchicine is now formally recommended only for these manifestations of BS, as is the case in the current European League Against Rheumatism (EULAR) recommendations[10].

We had looked at the longterm prognosis of patients who took part in a controlled trial of thalidomide during the early years of their disease[11]. We had noticed a tendency for less organ involvement in the long term among patients who had used colchicine during their posttrial followup period. However, it was not clear whether this observation reflected a real protective effect of colchicine or was confounded by prescription of colchicine to patients who appeared to have a milder disease course. This finding prompted us to look at the longterm prognosis of patients who had taken part in a double-blind, placebo-controlled trial of colchicine[8]. Our main hypothesis was that patients randomized to colchicine for 2 years during the initial years of their disease would need less immunosuppressive treatment as an indication for major organ involvement in the long term compared to patients randomized to placebo.

MATERIALS AND METHODS

The colchicine trial was a placebo-controlled, double-blind trial of 2 years' duration that recruited 60 male and 56 female patients between November 1991 and December 1995[8]. To be enrolled in the trial, the patients had to be between 18–35 years of age, to have less than 2 years' duration of disease, and to have active disease defined as the occurrence of oral or genital ulceration or erythema nodosum at least 3 times within the preceding 6 months. The trial enrolled 116 patients, of whom 84 completed the 24-month period.

Our dedicated multidisciplinary clinic meets once a week, and patients are evaluated regularly between 1 and 6 months depending on their clinical needs. Therapeutic decisions are made after discussion among the clinic members. The same was applied to the colchicine trial patients during their followup.

Between November 2009 and March 2010, a mean of 16.6 ± 1.1 years after the trial had ended, we invited the trial patients back to the clinic to reevaluate their outcome. We used a standard questionnaire that included questions about the clinical status of the patients at the time of evaluation, the development of major organ involvement during the posttrial period, and the use of immunosuppressives (azathioprine, cyclophosphamide, cyclosporine, tumor necrosis factor inhibitors, and interferon-α) at the posttrial period. Those who could not come to the clinic were interviewed by telephone using the same questionnaire. The information in hospital

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charts was used to confirm the answers to the questionnaire regarding the development of major organ involvement and the use of immunosuppressives including corticosteroids. We also used the information in hospital charts for patients who could not be contacted despite all attempts. All evaluations were performed with the examiners being masked to the original study groups of the patients. The local ethics committee of Cerrahpasa Medical School approved the study and all patients gave their consent before reevaluation.

The main study outcome was the use of immunosuppressive treatment for any indication during the posttrial period. We compared this among the group allocated to colchicine and among the group allocated to placebo in the original study, separately for men and women. Moreover, we also compared the use of immunosuppressives among patients according to the use of colchicine in the posttrial period.

Statistical analysis. The number of patients who used immunosuppressives among the colchicine group and among the placebo group in the original study were compared with a chi-square test. The number of patients who used immunosuppressives was also compared using a chi-square test among those who used colchicine during the posttrial followup and among those who did not. Duration of posttrial colchicine use and cumulative duration of colchicine use were compared using the Student's t test among those who used immunosuppressives and those who did not.

RESULTS

We evaluated 60 patients in the clinic and 30 patients through telephone calls. We could not contact 26 patients. Of those, 12 were lost to followup immediately after coming off the trial and 14 had attended the clinic a mean of 38.6 ± 28.8 (SD) months before being lost to followup. These 26 patients were excluded from the analyses because none of them had developed any major organ involvement during the time they attended the clinic. Thus, the completeness rate for the outcome information was 78% (90 of 116 patients). Table 1 illustrates the distribution of the patients according to the trial groups.

Immunosuppressive use. Twenty-eight patients (31%; 20 men and 8 women) had been prescribed immunosuppressives during the posttrial period (Figure 1). Fourteen of them (50%; 11 men, 3 women) were in the colchicine arm during the trial.

Fifty-eight patients (64%; 28 men) continued to take colchicine after the trial. Twenty (34%; 13 men, 7 women) received immunosuppressives during the posttrial period, while 10 were still using colchicine when an indication for starting immunosuppressives was made. Of the 32 patients (36%) who did not use colchicine after the trial, 8 (25%) received immunosuppressives during the posttrial period. There was no statistically significant difference regarding posttrial colchicine use and the initiation of immunosuppressives thereafter (p = 0.47; Table 2). The cumulative duration of colchicine use was also comparable between patients regarding the initiation of immunosuppressive treatment.

Table 1. The distribution of the patients at the time of reevaluation, according to their groups in the controlled trial (men, n = 30; women, n = 28). Data are n (%).

	Randomized to Colchicine, n = 58		Randomized to Placebo, n = 58	
	Men	Women	Men	Women
Contacted in the clinic	17 (57)	13 (46)	18 (60)	12 (43)
Contacted by telephone	8 (27)	6 (21)	8 (27)	8 (29)
Lost to followup	5 (17)	9 (32)	4 (13)	8 (29)

The most frequent indications for starting immunosuppressive treatment were arthritis (9 patients; 5 men, 4 women), followed by deep vein thrombosis (7 patients; 6 men, 1 woman) and CNS involvement (4 patients, all men). The indications for starting immunosuppressive treatment are listed in Table 3.

Steroid use. Twenty-four patients (colchicine arm 9, placebo arm 15) received corticosteroids during the posttrial period. In 19 patients they were used together with immunosuppressives. Five patients had used short-term corticosteroids irrespective of immunosuppressive use. Two of them were using colchicine when steroids were prescribed. The indications were arthritis in 4 and exacerbation of mucocutaneous lesions in 1.

Disease activity at the time of reevaluation. The disease had abated, defined as having no Behçet-related manifestation during the previous year, in 25 patients. Nine of them had used immunosuppressives before and 2 were still using an immunosuppressive. Three of these 9 patients were from the colchicine arm and 6 were from the placebo arm. In 1 patient, data regarding continuing manifestations were missing.

Among the lesions that had not abated, the only type of lesion that continued was oral ulceration in 17 patients. In 4 of these, the number of oral ulcers was ≤ 2 during the previous year. Additionally, 14 patients continued to have genital ulcers during the previous year, 25 continued to have papulopustular lesions, 17 continued to have nodular lesions, 11 continued to have episodes of arthritis, 2 had episodes of deep-vein thrombosis, 2 had active eye involvement, and 2 had active neurological involvement.

DISCUSSION

The design of our study enabled us to evaluate a group of patients at the long term who had similar disease characteristics at an early disease stage. Our data collection was quite satisfactory in that none of the 14 patients who had been lost to followup had used immunosuppressives during the time they were being followed in the clinic. Our results give a hint that continuous use of colchicine, even when initiated at an early disease stage, might not decrease the use of immunosuppressives at the long term. The indications for immunosuppressives and the number of patients with each type of major organ involvement were also somewhat similar between the colchicine and placebo arms. Half the patients who received immunosuppressives during followup had been randomized to colchicine during the trial. Moreover, irrespective of the treatment allocation in the original study, half of the patients were taking colchicine during the posttrial period when an indication for starting immunosuppressives occurred.

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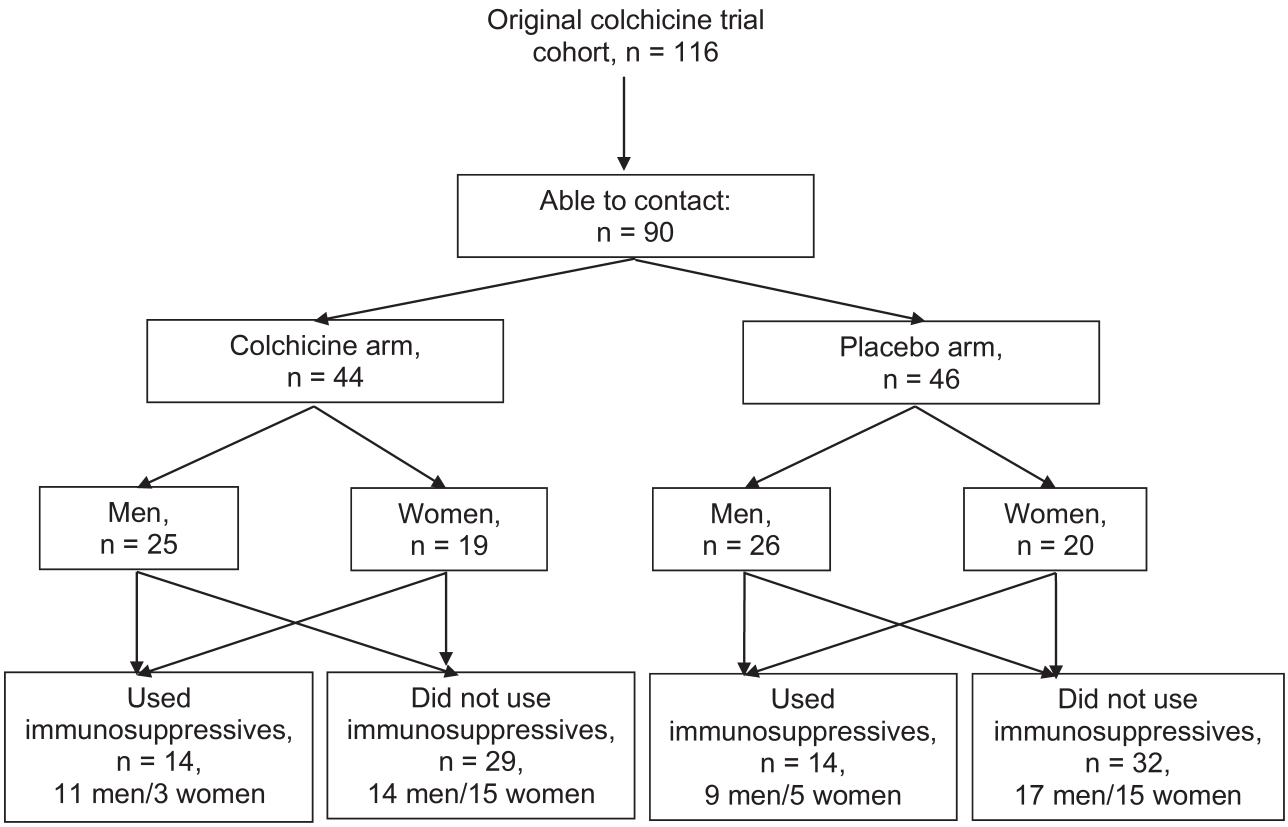

Figure 1. Immunosuppressive use according to sex and group allocations in the original trial.

Table 2. Patient characteristics according to the use of immunosuppressives during the posttrial period. Data are n (%), except where otherwise indicated.

Characteristics	Received Immunosuppressives	Did Not Receive Immunosuppressives	p
All patients, n = 90	28 (31)	62 (69)	—
Men, n = 51	20 (39)	31 (61)	0.069
Colchicine group, n = 25	11 (44)	14 (56)	0.129
Placebo group, n = 26	9 (35)	17 (65)	0.802
Women, n = 39	8 (21)	31 (79)	0.069
Colchicine group, n = 19	3 (16)	16 (84)	0.162
Placebo group, n = 20	5 (25)	15 (75)	0.592
Patients randomized to colchicine during the trial	14 (50)	30 (48)	1.0
Used colchicine after the trial	20 (71)	38 (61)	0.476
Total duration of colchicine use (trial + posttrial; mos, mean ± SD)	107.1 ± 53.4	99.9 ± 66.2	0.313
Duration of colchicine use during the trial (mos; mean ± SD)	22.1 ± 4.9	19.9 ± 8.0	0.772

In a previous survey with similar design, we looked at the longterm prognosis of patients who had taken part in a placebo-controlled, randomized trial of azathioprine[12]. Contrary to the findings of the current survey, we had seen that patients randomized to azathioprine had a better prognosis at the long term. It can be said that the mechanisms of action of colchicine and azathioprine are different and that the benefits of colchicine only appear when it is taken continuously. But we doubt this because of the long duration of cumulative colchicine use in our survey and because 50% of posttrial colchicine users were still taking colchicine when an indication for immunosuppressive treatment took place.

At the time of reevaluation, 42 patients (37%) had either no BS-related manifestation or only oral ulceration during the previous year. This is in line with our previous observa-

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Table 3. Indications for starting immunosuppressive treatment during the posttrial period.

Indications	Trial Group: Colchicine		Trial Group: Placebo	
	Men, n = 25	Women, n = 19	Men, n = 26	Women, n = 20
Eye involvement	—	1	—	1
Deep vein thrombosis	3	1	3	—
Pulmonary aneurysm	—	—	1	—
CNS involvement	2	—	2	—
GI involvement	1	—	—	1
Arthritis	2	1	3	3
Mucocutaneous involvement	2	—	—	—
Superficial thrombophlebitis	1	—	—	—

CNS: central nervous system; GI: gastrointestinal.

tions that the activity of BS abates with time[1,13]. Also, the fact that only 2 patients developed eye involvement during followup might be explained by the selection of patients with only mucocutaneous involvement and also with the early development of this complication during the course of BS.

Our study had several limitations. It was a retrospective design and we could not evaluate all patients in the clinic. On the other hand, we used a standardized questionnaire for all patients and confirmed the obtained information with the hospital charts. We had selected the use of immunosuppressives for any indication as an outcome measure rather than comparing the disease severity levels or rates of actual organ involvement between treatment groups. Also, the doses of the chosen drugs and the length of treatment may differ between indications. Our outcome measure is clinically relevant and assures a minimum threshold for the severity of complications. Another drawback is that the number of patients in the original trial was relatively small. Thus the need remains for a prospective, controlled, withdrawal study among colchicine responders.

Our survey again underlined the more severe disease course of BS among men[1]. The majority of the patients (71%) receiving immunosuppressives were men, and 39% of all men received immunosuppressives during followup. This number is similar to the 43% immunosuppressive use in the thalidomide survey, which enrolled only men with similar disease characteristics[11]. Taken together, these studies suggest that the risk for developing major organ involvement during the course of BS is around 40% for men even if they have only mucocutaneous disease at the early disease stage. It should be mentioned that this number was much higher among men developing BS at a young age (76% in the thalidomide study). These findings challenge current management strategies, such as EULAR recommendations, which primarily focus on the treatment of involved organs[10]. We believe that poor prognostic factors such as male sex, young age at the onset of BS, and frequent oral ulcerations should be the key considerations when initiating treatment for patients with early disease[14]. A placebo-controlled randomized study of azathioprine to test this hypothesis is currently recruiting patients at our center.

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