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Concise report

Prognosis of Behçet's syndrome among men with mucocutaneous involvement at disease onset: long-term outcome of patients enrolled in a controlled trial

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Abstract

Objective. To assess the influence of being free of major organ involvement during the early years of the disease on the prognosis of men with Behçet's syndrome (BS).

Methods. Ninety-six men with BS, who had only active mucocutaneous manifestations when entering a controlled trial of thalidomide mean (S.D.) 11.7 (0.8) years ago, were re-evaluated for the use of immunosuppressives as an indication of major organ involvement during the post-trial period.

Results. Outcome information was obtained in 91 (95%) patients. Thirty-nine (43%) patients had to use immunosuppressives during the post-trial period. Immunosuppressive use was significantly more frequent among patients developing BS at younger age (76%; $\leqslant$24 years) than older age (30%; $\geqslant$25 years). Developing BS at young age (OR = 6.3; 95% CI 2.09, 19.04) and not using colchicine during the post-trial period (OR = 3.860; 95% CI 1.484, 10.034) were risk factors for immunosuppressive use. However, 82% of the patients using colchicine had onset during old age. Colchicine showed a significant effect in decreasing the use of immunosuppressives only among patients of old age at onset (Fisher's exact test = 5.026; $P = 0.031$) in the subgroup analysis. Eye disease (18 patients) and vascular involvement (14 patients) were the most frequent indications for immunosuppressive use.

Conclusions. Being free of major organ involvement during the early years of BS does not indicate a mild prognosis for men developing BS at young age. Whether colchicine will reduce the need for immunosuppressive use among men developing BS at old age awaits formal studies.

Key words: Behçet's syndrome, Prognosis, Mortality, Thalidomide, Young, Cohort study, Uveitis.

Introduction

Behçet's syndrome (BS) is a systemic vasculitis of unknown aetiology characterized by the heterogeneous nature of organ involvement and a fluctuating disease course [1, 2]. It runs a more severe course among men and those developing the disease at a younger age, but predicting the clinical course and prognosis of the patients is not straightforward [3, 4]. In the clinical setting, the existing symptoms rather than the prognostic factors of the patients are taken into account for therapeutic decisions [5]. For example, a young male patient with predominant mucocutaneous manifestations and no organ involvement during the early years of his disease course is often considered to have a mild disease.

We had previously shown the efficacy of thalidomide in the treatment of mucocutaneous manifestations of BS in a double blind, randomized, placebo-controlled trial [6]. Since the patients in this trial had similar demographical

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and clinical characteristics, we thought that their re-evaluation in the long term would give valuable information about the clinical course of BS. Thus, we called these patients back to the clinic a mean of 11.7 years after coming off the trial. Our main interest was to assess the use of immunosuppressive drugs for any indication during the post-trial period, which had been one of the exclusion criteria of the thalidomide trial.

Methods

The thalidomide trial has been described in detail elsewhere [6]. Briefly, 96 male BS patients, all fulfilling the classification criteria [7] and who were aged between 18 and 35 years and had mean disease duration of 2.8 years, were randomized to receive either placebo or thalidomide 100 mg/day or 300 mg/day for 24 weeks between October 1993 and November 1996 [6]. Inclusion criteria were the presence of active mucocutaneous disease defined as having a minimum of two episodes of oral or genital ulcers within the 3 months before entering the study. Exclusion criteria were the presence of significant eye involvement resulting in any decrease in visual acuity, any organ involvement requiring immunosuppressive treatment, previous use of immunosuppressives and the presence of clinical neuropathy.

Between October 2006 and March 2007, we called these patients back to the clinic. Those who could not come to the clinic were either visited at their homes or interviewed by telephone calls. We used the information in hospital charts for patients who could not be reached despite all attempts.

We evaluated all patients with a form that included questions on the use of immunosuppressives (AZA, cyclosporine A, MTX, cyclophosphamide, IFN-α and TNF-α inhibitors) during the post-trial period. The use of colchicine during the post-trial period before the initiation of immunosuppressives was also noted. The examiners were masked to the original trial group allocations of the patients and all information was cross-checked with patient charts. The study was approved by the local ethics committee of Cerrahpasa Medical Faculty, and all patients gave their consent before re-evaluation.

The age at the onset of BS was defined as the age when the patient had fulfilled the classification criteria, and we obtained this information from the patient charts. We classified those patients developing BS at age $\leqslant$24 years as young onset (YO) patients and at age $\geqslant$25 years as older onset (OO) patients. We had used this classification in a former study that had looked at the influence of age at the onset and patient's sex on the severity of BS [8].

Statistical analysis

The main outcome of the study was the use of immunosuppressives during the post-trial period. The independent effects of all possible variables on the use of immunosuppressives were tested initially with univariate logistic regression analysis followed by multivariate logistic regression analysis using the backward stepwise method. A *P*-value of 0.05 was set to enter a variable, whereas a *P*-value of 0.10 was set to remove the variable from the model. Comparisons of the groups were done with Student's *t*-test or the Mann–Whitney U-test. The normality distribution of the variables was tested using one sample Kolmogorov–Smirnov test.

Results

Post-trial follow-up

We evaluated 49 patients in the clinic or at their homes and 26 patients with telephone interviews, a mean (S.D.) of 11.7 (0.8) years after they had come off the trial. We could not contact 21 patients. Four of them had died a mean (S.D.) of 6.2 (3.6) years after completing the trial and 12 had attended the clinic a mean (S.D.) of 5.4 (2.5) years during the post-trial period before being lost to follow-up. By using the data in the charts, we achieved outcome information in 91 (95%) of the 96 patients. The remaining five patients with no contact had been lost immediately after coming off the trial. They all were OO patients [mean (S.D.) age at onset 29.4 (1.9) years] with mean (S.D.) of disease duration 2.4 (2.2) years at entry to the trial. None of them had developed any complication requiring immunosuppressive treatment during their follow-up in our centre.

Patient characteristics

The study population consisted mainly of OO patients (66 patients; 73%). The mean (S.D.) age at the onset of BS was 21.2 (2.2) years for YO patients and 30.5 (3.4) years for OO patients ($P < 0.001$). The mean (S.D.) disease duration at entry to the thalidomide trial was similar between YO [2.6 (1.6) years] and OO patients [2.9 (2.1) years]. Signs of eye involvement (cells in the vitreous not affecting visual acuity) at entry to the thalidomide trial were significantly more frequent among YO (16 of 25; 64%) than OO patients (25 of 66; 38%; $P = 0.025$). Colchicine was used significantly more among OO (40 of 66; 61%) than YO patients (9 of 25; 36%; $P = 0.036$) during the post-trial follow-up.

Patients treated with immunosuppressives

Thirty-nine (43%) patients received immunosuppressives during the post-trial period. In the univariate analysis, young age at the onset of BS and not using colchicine were significantly associated with immunosuppressive use (Table 1). In the multivariate analysis, being a YO patient (OR = 6.3; 95% CI 2.09, 19.04) and not using colchicine during the post-trial period (OR = 3.860; 95% CI 1.484, 10.034) were significant risk factors for immunosuppressive use during the post-trial period. However, the vast majority (82%) of the patients using colchicine were OO patients. Because young age at the onset of BS was a strong risk factor for immunosuppressive use, we analysed the use of colchicine according to age at onset of the patients. This showed that colchicine significantly decreased the use of immunosuppressives among the OO (Fisher's exact test = 5.026; $P = 0.031$) but not YO patients (Fisher's exact test = 3.094; $P = 0.142$).

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Table 1 Characteristics of the patients according to the use of immunosuppressives during the post-trial period

	Received immunosuppressives	Did not receive immunosuppressives	*P*-value
All patients ($n = 91$), *n* (%)	39 (43)	52 (57)	
YO patients ($n = 25$)	19 (76)	6 (24)	<0.001
OO patients ($n = 66$)	20 (30)	46 (70)	
Had signs of eye disease at baseline[a] ($n = 41$), *n* (%)	22 (54)	19 (46)	0.094
YO patients ($n = 16$)	13 (81)	3 (19)	0.012
OO patients ($n = 25$)	9 (36)	16 (64)	
Did not have signs of eye disease at baseline[a] ($n = 50$), *n* (%)	17 (34)	33 (66)	
YO patients ($n = 9$)	6 (67)	3 (33)	0.047
OO patients ($n = 41$)	11 (27)	30 (73)	
Used colchicine during the post-trial period ($n = 49$), *n* (%)	13 (27)	36 (73)	0.001
YO patients ($n = 9$)	5 (56)	4 (44)	0.043
OO patients ($n = 40$)	8 (20)	32 (80)	
Did not use colchicine during the post-trial period ($n = 42$), *n* (%)	26 (52)	16 (38)	
YO patients ($n = 16$)	14 (88)	2 (12)	0.019
OO patients ($n = 26$)	12 (46)	14 (54)	
Age at onset of BS, mean (S.D.), years	25.4 (5.6)	29.9 (3.9)	<0.001
Disease duration at baseline[a], mean (S.D.), years	2.56 (1.63)	3.02 (2.15)	0.308

[a]Baseline: entry to the thalidomide trial.

Table 2 Indications for the use of immunosuppressives[a]

Indications	Number of patients	YO patients, *n* (%)	Age at onset of BS, mean (S.D.), years	Time to initiation of immunosuppressives afer coming off the thalidomide trial, mean (S.D.), years	Time to initiation of immunosuppressives from diagnosis, mean (S.D.), years
Eye disease	18	12 (67)	23.1 (4.3)	2.3 (4.7)	5.8 (3.9)
Vascular involvement	14	8 (57)	23.3 (5.2)	3.5 (3.0)	7.0 (3.7)
Superficial vein thrombosis	4	1			
Deep vein thrombosis	7	5			
Hepatic vein thrombosis	1	0			
Pulmonary aneurysm	2	2			
CNS involvement	4	1 (25)	26 (6.8)	3.6 (2.8)	5.7 (3.4)
Severe mucocutaneous manifestations	3	0	30 (3.6)	1.5 (1.2)	4.0 (1.3)
Frequent episodes of arthritis	2	0	32.5 (3.5)	1.8 (1.6)	3.8 (2.4)
Secondary amyloidosis	2	0	29 (1.4)	10.7 (1.9)	13.4 (0.6)

[a]Some patients had more than one indication.

Being allocated to thalidomide 100 mg (OR = 0.618; 95% CI 0.221, 1.73) or thalidomide 300 mg (OR = 0.458; 95% CI 0.165, 1.275) and having signs of eye involvement at entry to the trial (OR = 2.248; 95% CI 0.963, 5.248) were not associated with immunosuppressive use.

Indications for the use of immunosuppressives

The median duration from the end of the thalidomide trial until the initiation of immunosuppressives was 16 (95% CI 9.9, 22.1) months, and there was no significant difference between OO and YO patients. Eye disease and vascular involvement were the most common indications for the use of immunosuppressives and both occurred more frequently in YO patients (Table 2). Thirteen (72%) of the 18 patients receiving immunosuppressives for eye disease had signs of eye disease at the time of entry to the thalidomide trial and 10 (77%) of them were YO patients. The first ocular attack causing more than two lines drop in visual acuity had occurred at a mean (S.D.) of 2.3 (4.7) years during the post-trial follow-up. In the original trial, the development of new eye disease and impairment in visual acuity were observed less frequently in both thalidomide arms compared with placebo [6]. We therefore looked at 13 patients who had signs of eye disease and developed serious eye involvement later on. Seven of these patients were in the placebo arm and six

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were in the thalidomide arms. Ocular signs had not regressed in any of these patients during treatment with thalidomide.

One patient with eye disease developed end-stage renal disease as an adverse effect of cyclosporin A and underwent successful renal transplantation. This patient is still under follow-up, now being 6 years after the transplantation. All four patients with CNS involvement had parenchymal type disease with one having co-existing eye involvement and amyloidosis.

Mortality

Four (two being YO) patients had died during the post-trial period. The causes of death were bleeding of a pulmonary aneurysm, hepatic encephalopathy due to Budd Chiari syndrome and sepsis in a patient with amyloidosis. One death was unrelated to BS.

Patients not treated with immunosuppressives

Fifty-two (57%) patients did not use immunosuppressives during the post-trial period and 46 (88%) of them were OO patients. Fourteen (27%) of these 52 patients did not receive any systemic medication during the follow-up, 32 (62%) received colchicine for mucocutaneous manifestations and 6 received NSAIDs or SSZ for joint pain and/or arthritis.

Discussion

We evaluated the long-term course of BS in a group of men who had no major organ involvement during the early years of their disease. Our results suggest that age at onset of the disease, but not the initial clinical presentation, determines the long-term prognosis of men with BS. All our patients had similar clinical characteristics during the first 3 years of their disease course, but YO patients developed significantly more complications requiring treatment with immunosuppressives during follow-up compared with OO patients. Our results also suggest a possible effect of colchicine in reducing the need for immunosuppressive use among OO patients.

The information on the more severe course of BS among men and YO patients is not new and has been repeated in several studies [2, 9, 10]. However, these studies evaluated patients with heterogeneous clinical manifestations and variable disease durations. Our study differs from these studies with its homogeneous patient population in terms of clinical and demographic characteristics. Furthermore, the selected outcome measure, the use of immunosuppressives for any indication during follow-up, is clinically relevant and assures a minimum threshold for the severity of complications.

Most of the YO patients (76%) required immunosuppressive treatment compared with 30% of OO patients. Even having signs of eye involvement had no impact on the later requirement for immunosuppressives. These results suggest that age at onset of BS, rather than the presence or absence of organ involvement, needs to be considered at the first line when planning the treatment for a male patient during the initial years of BS. This view is supported by a previous survey from our centre that showed a better long-term outcome for men when treated with AZA earlier in their disease course [11].

Colchicine is an alkaloid that inhibits several actions of neutrophils and the increased neutrophil activity in BS makes the widespread use of colchicine logical for this disease [12]. However, formal data on the efficacy of colchicine in BS are limited to only two trials that showed only a modest effect [13, 14]. The earlier study [13] was limited to men, whereas the later [14] showed a better efficacy of colchicine among women. This gender different efficacy was also evident in our double blind trial of depot-steroids [15]. These observations could simply reflect the well-known less severe course in women. In the current survey, colchicine appeared to decrease the requirement for immunosuppressive use among OO patients. This could also be taken to support the contention that colchicine works better among patients with less severe disease—the older onset in the current study [8]. However, this novel finding should still be interpreted with caution because of our group's inclination to use colchicine almost only in patients expected to have a milder disease course. We think that a withdrawal trial with colchicine would help to clarify this finding.

In conclusion, men developing BS at young age have an increased risk of developing severe disease even if they are free of major organ involvement during the initial years of their disease. These findings challenge our current treatment strategy of BS, at least in men developing BS at young age.

Rheumatology key messages

- Men developing BS at young age have increased risk for a more severe outcome.
- Being free of major organ involvement at onset is not a sign of a favourable outcome.
- Whether colchicine reduces the use of immunosuppressives warrants further studies.

Disclosure statement: The authors have declared no conflicts of interest.

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