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Behçet Disease With Vascular Involvement

Effects of Different Therapeutic Regimens on the Incidence of New Relapses

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Abstract: Vascular involvement is one of the major causes of mortality and morbidity in Behçet disease (BD). There are no controlled studies for the management of vascular BD (VBD), and according to the EULAR recommendations, only immunosuppressive (IS) agents are recommended. In this study, we aimed to investigate the therapeutic approaches chosen by Turkish physicians during the initial event and relapses of VBD and the association of different treatment options with the relapses retrospectively.

Patients with BD (n = 936, female/male: 347/589, mean age: 37.6 ± 10.8) classified according to ISG criteria from 15 rheumatology centers in Turkey were included. The demographic data, clinical characteristics of the first vascular event and relapses, treatment protocols, and data about complications were acquired.

VBD was observed in 27.7% (n = 260) of the patients during follow-up. In 57.3% of the VBD patients, vascular involvement was the presenting sign of the disease. After the first vascular event, ISs were given to 88.8% and AC treatment to 59.8% of the patients. Median duration of AC treatment was 13 months (1–204) and ISs, 22 months (1–204). Minor hemorrhage related to AC treatment was observed in 7 (4.7%) patients. A second vascular event developed in 32.9% (n = 86) of the patients. The vascular relapse rate was similar between patients taking only ISs and AC plus IS treatments after the first vascular event (29.1% vs 22.4%, $P = 0.28$) and was significantly higher in group taking only ACs than taking only ISs (91.6% vs 29.1%, $P < 0.001$). During follow-up, a third vascular event developed in 17 (n = 6.5%) patients. The relapse rate was also similar between the patients taking only ISs and AC plus IS treatments after second vascular event (25.3% vs 20.8%, $P = 0.93$). When multivariate analysis was performed, development of vascular relapse negatively correlated with only IS treatments.

We did not find any additional positive effect of AC treatment used in combination with ISs in the course of vascular involvement in patients with BD. Severe complications related to AC treatment were also not detected. Our results suggest that short duration of IS treatments and compliance issues of treatment are the major problems in VBD associated with vascular relapses during follow-up.

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Abbreviations: AC = anticoagulant, BD Behçet = disease, EULAR = European League Against Rheumatism, INR = international normalized ratio, IS = immunosuppressive, ISG = International Study Group, VBD = vascular Behçet disease.

INTRODUCTION

Behçet disease (BD) is a systemic disease characterized by oral aphthosis, genital ulcers, ocular lesions, and systemic involvement including gastrointestinal, musculoskeletal, neurological, and major vessels. Vasculitis is a main pathologic finding in BD. Vessels of all sizes can be involved, in both the arterial and venous systems,[1,2] with venous and arterial occlusions and arterial aneurysms.[3]

Vascular involvement is observed in up to 40% of the patients with BD, especially in young men, and is one of the major causes of mortality and morbidity.[4] Although venous thrombosis is seen primarily in the lower extremities, it may affect many different sites including the inferior and superior vena cava, pulmonary artery, suprahepatic vessels, and cardiac cavities.[5] Up to 17% of the mortality in BD is reported to be associated with venous involvement such as pulmonary embolism or Budd–Chiari syndrome.[6] In a recent study from Turkey, it was shown that 35.4% of patients with vascular BD (VBD)

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had recurrent vascular events in follow-up. New vascular event development risk was 23.0% at 2 years and 38.4% at 5 years.[7]

The primary pathology leading to venous thrombosis in BD is the inflammation of the vessel wall. Systemic immunosuppressives (ISs) are used to reduce this inflammation. However, there is no controlled study for the management of VBD. According to the EULAR recommendations for the management of BD, for acute deep vein thrombosis in BD, IS agents such as corticosteroids, azathioprine, cyclophosphamide, or cyclosporine A are recommended. For the management of pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended. Despite a high frequency of venous thrombosis, as pulmonary embolism is rare and a coexisting pulmonary aneurysm might result in fatal bleeding, anticoagulants (ACs), antiplatelet, or antifibrinolytic agents are not recommended.[8] There are very limited data about anticoagulation in the treatment of deep venous thrombosis associated with BD. In this study, we aimed to investigate the therapeutic approaches chosen by Turkish physicians during the initial event and relapses of VBD and the association of different treatment options with the relapses, retrospectively.

METHODS

In this retrospective study, 936 patients (woman/man: 347/589, mean age: 37.6 ± 10.8 years) classified according to ISG criteria[9] from 15 rheumatology centers in Turkey, were included. Mean disease duration was 7.9 ± 6 years. Median follow-up during the study was 48 (1–376) months. The demographic data, clinical characteristics of first vascular event and relapses, treatment protocols, and data about complications were acquired from patient files, retrospectively. Treatment protocols were mainly defined as IS agents (corticosteroids: 0.5–1 mg/kg, methotrexate: 15–25 mg/week, azathioprine: 2–2.5 mg/kg, cyclophosphamide: 500–1000 mg/mo, 6–9 pulses, infliximab: 5 mg/kg, every 8 weeks or interferon-α: 3.0 million IU (MIU)/day, SC for 14 days as induction, and 3.0 MIU 3/week SC for maintenance) and ACs (warfarin, conventional and low-molecular-weight heparin). In routine practice of experienced centers in Turkey, conventional or low-molecular-weight heparin is generally replaced with oral warfarin within 2 to 4 weeks. Study protocol was approved by Marmara University, School of Medicine Local Ethics Committee, and the study was performed according to the Declaration of Helsinki.

Statistical data were performed with Statistical Package for the Social Sciences 16.0 (SPSS, Chicago, IL) program. Results were expressed as means and standard deviations or as median (minimum-maximum) according to the distribution of data. Independent-samples *t* test, χ^2 test were used for comparisons of data. Spearman correlation test was used to analyze correlations. Logistic regression analysis was performed to determine the effects of treatment protocols and the disease manifestations on vascular relapse rate.

RESULTS

Mucocutaneous disease was present in 363 patients (38.7%), whereas 573 patients (61.3%) had major organ involvement (ocular involvement [OI]: 42.5%, arthritis: 26.7%, neurological involvement [NI]: 7.6%, and gastrointestinal involvement: 2%).

VBD developed in 27.7% (n = 260) of the patients during follow-up. The majority of patients with VBD were men (86.2%, n = 224). Thrombophilic factors were investigated in 34.9% (n = 88), and 38.7% (n = 34) of these patients had thrombophilic disorders. When the first vascular event developed, median disease duration was 0 (0–28) years and mean age was 32.3 ± 9.5 years. In 57.3% of the VBD (n = 149) patients, vascular involvement was the presenting sign of the disease. A second vascular event was observed in 9.2% (n = 86) of the whole group, a third vascular event in 1.8% (n = 17), and a fourth vascular event in only 3 patients.

When we looked at the subtypes of vascular involvement, 84.6% of VBD (n = 220) patients had only venous disease, 8.1% (n = 21) had only arterial disease, and 4.2% (n = 11) had both venous and arterial diseases. Eight patients (3.1%) had cardiac involvement. In venous involvement group, the most frequent form was deep venous thrombosis of the lower extremities (70.5%). When we looked at the rare vascular forms of BD, pulmonary aneurysm was present in 11.2% (n = 29), vena cava superior or inferior thrombosis in 8.5% (n = 22), pulmonary thrombosis in 2.7% (n = 7), and Budd–Chiari syndrome in 1.2% (n = 3) (Table 1).

When the first vascular event occurred, 16.5% of patients were on IS treatments due to other major organ involvements. After the first vascular event, corticosteroid therapy was given to all VBD, IS treatment was given to 88.8%, and AC treatment to 59.8% of the patients (Figure 1). Median duration of anticoagulation was 13 months (1–204) and immunosuppressives 22 months (1–204). After the first event, azathioprine was given to 66.7% (n = 166) of the VBD group, cyclophosphamide to 29.7% (n = 74), infliximab to 7.2% (n = 18), and methotrexate to 0.8% (n = 2). Minor hemorrhage (as a complication related to AC treatment) was observed in 4.7% (n = 7) patients (4 gastrointestinal bleeding, 1 epistaxis, 2 subcutaneous hematoma) without a major adverse event.

RELAPSES IN VBD

First vascular relapse developed in 32.9% (n = 86) of VBD patients. The time interval between the first and second vascular events was 25.5 (1–252) months. When this first relapse developed, 16.3% (n = 14) of the patients were only on AC treatment and 32.6% (n = 28) were untreated. Between patients with and without a relapse in the follow-up, duration of AC and IS treatments were similar ($P = 0.15$ and $P = 0.10$). However, relapse was significantly lower in patients taking ISs (25.3% vs 85.7%, $P < 0.001$), whereas observed higher in the group

TABLE 1. Clinical Characteristics of Vascular Behçet Disease (n = 260)

Gender	
Male (n = 224)	86.2%
Age during first vascular event (years)	32.3 ± 9.5
Only venous disease (n = 220)	84.6%
Only arterial disease (n = 21)	8.1%
Both venous and arterial disease (n = 11)	4.2%
Cardiac involvement (n = 8)	3.1%
Rare vascular involvements	
Budd–Chiari syndrome (n = 3)	1.2%
Pulmonary aneurysm (n = 29)	11.2%
Pulmonary thrombosis (n = 7)	2.7%
Vena cava superior or inferior involvement (n = 22)	8.5%
Second vascular event (n = 86)	32.9%
Third vascular event (n = 17)	6.5%
Fourth vascular event (n = 3)	1.1%

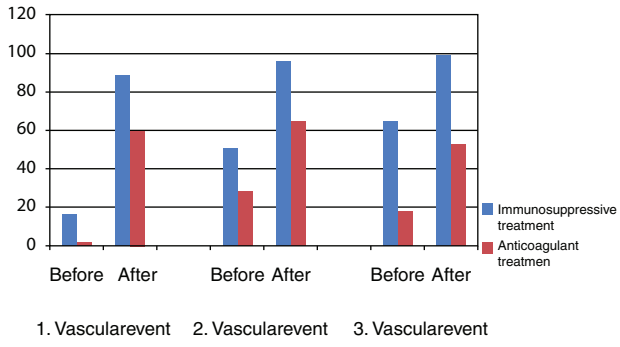

FIGURE 1. Treatment of vascular events during the follow-up.

taking only ACs (91.6% vs 29.1%, $P < 0.001$). The rate of new vascular event development was similar between the patients taking only ISs and AC plus IS treatments (29.1% vs 22.4%, $P = 0.28$). No significant differences in relapse rate was also observed between the patients having thrombophilic factors or not (47.2% vs 28.8% $P = 0.08$). When we analyzed the vascular relapse rate according to other major organ involvements, we did not find any association (Table 2). We also did not observe any difference in subtypes of vascular involvement regarding vascular relapse.

After the second vascular event, IS treatment was given to 96.5% and AC treatment to 64.7% of the patients. During follow-up, a second relapse developed in 17 (6.5%) patients. The rate of new vascular event development was, again, similar between the patients taking only ISs and AC plus IS treatments after the second vascular event (25.3% vs 20.8%, $P = 0.93$). In only 3 patients, a third relapse occurred.

There was no relationship between the total duration of AC treatment and number of vascular events. However, the total number of vascular events negatively correlated with the age during the first vascular event (r: −0.179, $P = 0.005$). When multivariate analysis was performed, development of vascular relapse negatively correlated with only IS treatments ($\beta = -3.432$, SE = 0.886, $P < 0.000$). We did not observe any association with relapse rates and AC treatment ($\beta = -0.536$, $P = 0.397$), age ($\beta = -0.027$, $P = 0.429$), gender ($\beta = -0.470$, $P = 0.614$), presence of thrombophilic factors ($\beta = 0.854$, $P = 0.142$), arthritis ($\beta = 0.607$, $P = 0.377$), ocular involvement ($\beta = 0.322$, $P = 0.598$), or neurological disease ($\beta = 0.282$, $P = 0.701$).

TABLE 2. Vascular Relapse Rate According to Other Major Organ Involvements

		Relapse Rate (%)	*P* Value
Arthritis	Positive (n = 24)	38.9	0.332
	Negative (n = 206)	31.5	
Ocular	Positive (n = 108)	37	0.285
	Negative (n = 152)	30.3	
Neurological	Positive (n = 22)	50	0.097
	Negative (n = 238)	31.5	
Gastrointestinal	Positive (n = 7)	42.8	0.688
	Negative (n = 253)	32.8	

DISCUSSION

In the present study, we did not observe any additional positive effect of AC treatment (added on to IS treatments) to prevent relapses in the course of vascular involvement. Although, EULAR recommendations do not suggest routine usage of anticoagulants, surveys among Behçet's experts show that these recommendations are not possibly reflecting the routine practice. In a survey study, a significant subset of physicians still choose to use ACs as a major therapy in VBD; AC was preferred by 87% among physicians from USA/Israel and 40% in Turkey.[10] Supporting this survey, the present study showed that, although not recommended, a significant subset (30%–60%) of patients with VBD in Turkey are anticoagulated.

In addition to the lack of controlled trials, there are few large series in the literature investigating the role of various therapeutic options in VBD. In a large French series analyzing a retrospective cohort of 807 BD patients, all patients with deep vein thrombosis (n = 296) received anticoagulation therapy despite a high number of associated arterial aneurysms (n = 44); 8 of which were pulmonary. Hemorrhagic complications were observed only in 2% of the patients. The rate of IS usage was only 46.8% in patients having VBD in this study. Similar to our observations, IS agents significantly reduced venous thrombosis relapses in this study.[11] However, lack of a group with only IS therapy limits the interpretation of the results.

Ideguchi et al reported quite lower frequency of VBD in Japan as 6%, compared to other ethnic populations. In Japan series, IS treatments were given to all patients. Nine of 26 patients with VBD received warfarin, without bleeding complications.[12] Ahn et al, in a retrospective analysis of 37 patients, observed that recurrence of venous thrombosis occurred in 2 cases in the IS-only group (12.5%), 1 case in the combination therapy group (5.9%), and 3 cases in the AC group (75%), without a significant difference between the IS and combination therapy groups.[13] Ozguler et al, in a prospective follow-up of 39 patients, reported vascular relapses in 17 (44%) patients having only IS therapy during a follow-up period of 19.2 months.[14] In our study, vascular relapse developed in 32.9% of VBD patients with a median follow-up of 25.5 months. Only 50% to 60% of patients were under IS treatments before relapses, suggesting that short duration of IS treatment is (possibly) the major cause of relapses during follow-up. In a retrospective follow-up of 258 BD patients (mean follow-up duration: 45.8 months), we observed that prevalence of patients without any treatment due to inefficacy, compliance problems, or side effects changed between 6.4% and 45% in consecutive visits.[15] Therefore, compliance issues can be a reason of 'short duration' of treatment in VBD. However, in EULAR or in any other management guideline, it is also not clear how long the duration of treatment should be in VBD patients taking IS agents. Most physicians are possibly reluctant to use ISs more than 2 years. However, our results imply that duration of treatment must be longer to prevent new vascular events in VBD.

In our study, the relapse rate in patients having thrombophilic factors was higher, but without reaching the statistical significance. In another study from Turkey, among 96 patients with thrombosis, patients with recurrent thrombotic events had a significantly higher incidence of thrombophilias than those patients with only 1 thrombotic event.[16]

Major limitation of our study is its retrospective design. Severity of vascular disease is also not assessed with a standard

instrument, as there is none validated for the assessment of VBD. Lack of data about the efficiency of INR monitorization during AC treatment is another limitation.

In conclusion, we did not find any additional positive effect of AC treatment used in combination with ISs in the course of vascular involvement in patients with BD. A major cause of relapses seems to be early termination of IS therapies in our group. Although not supported in this analysis, the exact role of AC treatment in the long-term course of VBD can only be clarified with randomized, controlled, prospective studies, investigating course of vascular insufficiency and vascular quality of life in addition to relapses. Until then, long-term ISs should stay as the main treatment option in VBD.

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