Vascular Behçet's disease: a comparative study from Turkey and France

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Abstract

Objective

Vascular Behçet's disease (VBD) is a systemic vasculitis involving both arterial and venous vessels of all sizes and occurring in up to 40% of patients with BD. VBD is the main cause of mortality in BD. Although commonly seen around the Mediterranean region, comparative studies in VBD are lacking. We aimed to compare the course and therapeutic approaches of VBD in two large cohorts from Turkey and France.

Methods

We included 291 VBD patients (female/male:63/228, mean age: 41.2±11.3 years) who were followed up in the Department of Internal Medicine and Clinical Immunology at Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France (n=131) and Rheumatology Division of Marmara University School of Medicine, Istanbul, Turkey (n=160). All clinical and demographical data were acquired from patient charts retrospectively.

Results

*Smoking, family history for BD, HLA-B*51 presence and pathergy positivity were significantly higher in Turkish patients (TR), while neurologic involvement was more prominent in the French (FR) group. After a median follow-up of 77 months, 562 vascular events occurred including 440 venous events, 115 arterial events and 7 cardiac thrombi. In 79 (29%) patients, first vascular event developed before BD diagnosis and for 77 (28%) of them, vascular involvement was the presenting sign of the disease. First relapse developed in 130 (44.7%) patients after median 24.5 (1-276) months of follow-up (TR: 46.3% (n=74), FR: 42.7% (n=56), p=0.56). Survival graph revealed that FR cohort has 1.64 times increased recurrent event risk compared to TR cohort (HR=1.64 (1.1-2.44), p=.014) and although did not reach to statistical significance, IS treatment after the first vascular event decreased further vascular events (HR= 0.66 (0.43-1.01, p=.057).*

Conclusion

Almost half of patients relapsed of VBD within 2 years after the first vascular event. Immunosuppressants decrease VBD relapses.

Key words

vascular Behçet's disease, relapse, treatment, immunosuppressives, anti-coagulation

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Introduction

Behçet's disease (BD) is a systemic inflammatory disease characterised by oral and genital ulcers, and systemic involvement including ocular, neurological, gastrointestinal and musculoskeletal system. Vasculitis is the one of major histopathological findings of BD (1). Vascular involvement of Behçet's disease (VBD) involves both arterial and venous vessels of all sizes (2), and defined as a 'variable-vessel vasculitis' in Chapel-Hill consensus classification. VBD is observed in up to 40% of patients with BD (3-5). However, vascular involvement is quite rare in East Asia countries such as Japan and Korea (<10%) (6, 7). VBD is the main cause of mortality in BD. Up to 17% of the mortality is reported to be associated mainly with Budd-Chiari syndrome, pulmonary aneurysm and/or embolism (8).

Deep venous thrombosis of lower extremities is the most common form of VBD (up to 80%). Femoral (superficial, deep, and common) and popliteal veins are the most frequently involved veins, and are followed by crural, external iliac, and common iliac veins. However, many other sites including vena cava inferior and superior, pulmonary arteries, supra-hepatic vessels, dural/sagittal sinuses and cardiac cavities may also be involved. Despite immunosuppressive (IS) treatment, one third of VBD patients relapsed in retrospective series (3-5). Ozguler *et al*. reported that almost half of the VBD relapsed during 24 months under IS treatment in a prospective follow-up of 33 patients with DVT in lower extremities (9). Post-thrombotic syndrome (PTS) is the most common complication of DVT and is associated with varying combinations of leg pain, heaviness, swelling, oedema, hyperpigmentation, and varicose collateral veins. PTS also impairs quality of life (QoL) (10) and was detected in more than half of BD patients with DVT (11, 12).

IS treatment is the mainstay of VBD. There is no consensus for anticoagulation. According to EULAR Recommendations, anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out (13). On the other hand, anticoagulation is recommended in the treatment of venous thromboses after evaluation of arterial aneurysm presence in French recommendations for management of BD (14).

Although commonly seen around the Mediterranean, comparative studies in VBD are lacking. In this study, we aimed to compare the course of vascular BD, therapeutic approaches during the initial event and relapses of VBD and the association of different treatment options with the relapses in two large cohorts from Turkey and France.

Material and methods

We retrospectively included 291 VBD patients (female/male: 63/228) who were followed up in the Department of Internal Medicine and Clinical Immunology at Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France (n=131) and Rheumatology Division of Marmara University School of Medicine, Istanbul, Turkey (n=160). All patients fulfilled ISG criteria for BD (15). Retrospective data (demographic data, clinical characteristics of first vascular event and relapses and treatment protocols) were acquired from patient charts. Patients were routinely evaluated every 3 months and more frequent if there is an acute symptom. Treatment protocols were mainly defined as IS agents (corticosteroids, methotrexate, azathioprine, cyclophosphamide, infliximab or interferon-α) and ACs (conventional and low molecular- weight heparin followed by oral anticoagulants). At least one month of IS/AC treatment was necessary for the patient to be accepted as IS/AC treated.

Any new vascular event developed after the first vascular event was described as relapse. This new vascular event could be at the same or different vessel diagnosed by both a new positive clinical sign and with imaging modalities (Doppler US for DVT diagnosis, BT angiography for pulmonary/peripheric arterial involvement and cerebral MR and MR angiography for cerebral vessel involvement).

If available, thrombophilia factors were also recorded. Thrombophilia

was defined as presence of Factor-V Leiden, prothrombin gene mutations or positive anticardiolipin antibodies.

The reference point for follow-up time was the diagnosis of BD. If the first vascular event was before the diagnosis, time for first vascular event was accepted according to the patient's statement.

The institutional review board of the Marmara Medical School approved the present study (approval no. 09.2017.530) and the study was performed according to the Declaration of Helsinki. The written informed consent was not required due to study's design as being a retrospective chart review.

Table I. Clinical characteristics of patients with vascular Behçet's disease.

	All patients (n=291)	Turkish patients (n=160)	French patients (n=131)	*p*
Male, %	228, 78.4%	132, 82.5%	96, 73.3%	0.064
Age at diagnosis (years, n=281)	29.1 ± 8.8	29.3 ± 8.1	28.8 ± 9.7	0.590
Mean age at first vascular even t (n:274)	30.9 ± 9	32 ±9.1	29.4 ± 8.8	**0.016**
Smoking ever, % (n=165)	91, 55.2%	63, 63%	28, 43.1 %	**0.016**
Family history for BD, % (n=215)	47, 21.9 %	42, 29.2 %	5, 7.0 %	**<0.001**
HLA B51 positivity, % (n=113)	51, 45.1 %	16, 64 %	35, 39.8 %	**0.041**
Pathergy positivity, % (n:172)	91, 52.9 %	84, 60.4 %	7, 21.2 %	**<0.001**
Eye involvement, %	41.6 %	38.8 %	45 %	0.285
Neurological involvement, %	24.1 %	13.8 %	36.6 %	**<0.001**
Neurologic parenchymal	23, 32.9%	7, 31.8%	16, 33.3%	**0.999**
Neurologic vascular	47, 67.1%	15, 68.2%	32, 66.7%	
GIS, %	2.9 %	3.1%	2.4%	0.999
Follow up time* (months)(n=277)	132 (66-204)	120 (60-180)	144 (72-240)	**0.027**
IS treatment during first vascular event, % (n=27)	11.7 %	15.4 %	4 %	**0.015**

* (median, 25-75%). BD: Behçet's disease; GIS: gastrointestinal involvement; IS: immunosuppressive.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were tested for normality assumption with histogram, normal quantile plot, Kolmogorov Smirnov, and skewness kurtosis tests. Continuous variables without normal distribution were presented with median, 25–75%, minimum and maximum values. Continuous variables were compared between the groups by using Mann Whitney U and Kruskal Wallis tests. Correlations between continuous variables were evaluated with Spearman test, where both rho and *p*-values were reported.

We developed univariate Cox regression models for the recurring vascular events where time intervals to the first vascular event or between two vascular events were defined as time variable. Each vascular event or end of observation period were defined as end of time variable. Vascular events were defined as failure events. For this analysis, we created a longitudinal database for recurring events, where the intervals related to those events were arranged as observations (or rows) in our database. Each interval had a start and an end point and contained information whether this interval resulted with a vascular event. Each patient with recurring vascular events had multiple intervals for recurring events. For regression model, the initial independent variable was the centre categories (either French or Turkish patients). Then the regression models were repeated for both patient strata by using immunosuppressive treatment after first vascular event as independent variable. Hazard ratios with 95% CI interval and p values were reported for each model. Follow up duration was defined as time interval between diagnosis and last follow-up time. Therefore, patients with first vascular event before diagnosis were excluded from analysis.

All statistics and visualisation steps were performed with SPSS v. 21.0. (IBM Corp, Armonk, NY) and Stata 15.1 software (StataCorp, Texas, USA).

Results

In this retrospective study, 291 patients with VBD (female/male: 63/228, mean age: 41.2±11.3 years) from France (FR) and Turkey (TR), were included. Median diagnosis year for French patients and Turkish patients were 1995 (min/max: 1975–2019) and 2008 (min/max: 1978–2017) respectively. Median disease duration was 11 (0–38) years at the last follow-up visit. Clinical characteristics of patients were given in Table I. Smoking, family history for BD, HLA-B*51 presence and pathergy positivity were significantly higher in Turkish patients, while neurologic involvement was significantly higher in FR group. Thrombophilia factors were investigated in 47.4% (n=138), and 16% (n=22) of these patients had a thrombophilic disorder.

Minor haemorrhage (as a complication related to AC treatment) was observed in 2.4% (n=4) of Turkish cohort patients (all gastrointestinal bleeding) without a major adverse event (no need for intervention or hospitalisation and resolving with anticoagulation cessation). There was no data for anticoagulant complications in FR cohort.

Nine VBD patients (3%) died during follow-up (3 in TR cohort, 6 in FR cohort). Two patients died due to Budd-Chiari syndrome, 1 due to coronary aneurysm rupture in TR cohort. One patient died because of digestive neoplasia, but the cause of mortality for the remaining 5 patients from FR cohort was unknown. Median follow-up duration was 132 (66–204) months. Totally 562 vascular events occurred during the follow-up period. When we looked at the subtypes of vascular involvement, 440 venous events, 115 arterial events and 7 cardiac thrombi occurred (Table II). Median number of vascular events were not different between centres (1(1–4) *vs*. 1(1–6), p=0.769).

There were some important differences between the FR and TR cohorts for type of vascular involvement. Lower limb DVT was more common in Turkish group, whereas vena cava thrombosis, BCS and CVT were more frequent in French patients. Among arterial events only pulmonary thrombi was more common in Turkish group.

When the first vascular event developed, mean age of VBD patients was 30.9±9 years. In 79 (29%) patients, first vascular event developed before BD diagnosis and for 77 (28%) of patients,

vascular involvement was the presenting sign of the disease. The first vascular event occurred before BD diagnosis in 44.3% of the FR patients, while it occurred before BD diagnosis in only 17.8% of TR patients (p<0.001).

After the first vascular event, the rate of IS treatment was significantly higher in TR cohort compared to FR cohort (87.5% *vs*. 64.3%, p<0.001), whereas AC treatment was significantly higher in FR cohort (89.1% *vs*. 43.8%, p=<0.001), possibly associated with the vascular event as the sole presence. During first vascular event, 27 (11.7%) patients were under the IS treatment for any reason other than vascular involvement. After the first vascular event, IS treatment was given to 223 patients (77.2%), in 170 (59.2%) of these patients, glucocorticoid treatment was also given. AC treatment was given to 64 % (n=185) of the patients. After the first event, azathioprine was given to 60% (n=177) of the VBD group, cyclophosphamide to 14.3% (n=41) and TNF inhibitors to 5.5% (n=16).

Relapses

The first relapse developed in 130 (44.7%) patients after median 24.5 (1-276) months of follow-up. The relapse rate was 46.3% (n=74) in TR cohort and 42.7% (n=56) in FR cohort (p=0.556). When the first relapse developed, only 43.5% of patients were under IS treatment (25.3% with AC) and 40.7% of patients were not taking any treatment. After first vascular relapse five patients (4%) had no treatment, and 37 (29.6%), 19 (15.2%), 64 (51.2%) of patients were treated with IS, AC and IS+AC respectively. Relapse rate was significantly lower in patients given only ISs compared to given only AC after first vascular event (34.3% *vs*. 75.9%, p<0.001). There was no benefit of adding ACs on IS treatment regarding relapse rate (34.3% *vs*. 36.2%, p=0.879). We grouped patients (who were under IS treatments) into 3 groups as only corticosteroids (n=29, prednisolone >10mg/day), conventional ISs with or without corticosteroids (n=176) or TNF inhibitors (n=16) after the first vascular event. All treatments significantly decreased vascular relapse rate compared to pa-

Table II. Distribution of vascular events.

Types of vascular involvement	Turkish patients (n=160)	French patients (n=131)	*p*
Arterial	22 (13.7%)	2 (1.5%)	**<0.001**
Venous	115 (71.4%)	89 (66.8%)	0.605
Arterial + venous	23 (14.3%)	39 (29.2%)	**0.001**
Cardiac	1 (0.6%)	6 (4.5%)	**0.048**
Location/Types of venous involvement			
Superficial venous thrombi	23 (8.5%)	13 (4.5%)	0.059
Lower limb (deep vein thrombi)	142 (52.2%)	105 (36.2%)	**<0.001**
Vena cava thrombi	5 (1.8%)	25 (8.6%)	**<0.001**
Budd Chiari syndrome	2 (0.7%)	14 (4.8%)	**0.004**
Cerebral venous thrombi	23 (8.5%)	43 (14.8%)	**0.025**
Others	10 (3.7%)	20 (6.9%)	0.095
Location/Types of arterial involvement			
Pulmonary aneurysm	3 (1.1%)	2 (0.7%)	0.677
Pulmonary thrombi	49 (18%)	28 (9.7%)	**<0.001**
Aorta aneurysm/thrombi	4 (1.5%)	4 (1.4%)	0.999
Other (coronary, peripheric)	6 (2.2%)	19 (4.8%)	0.113

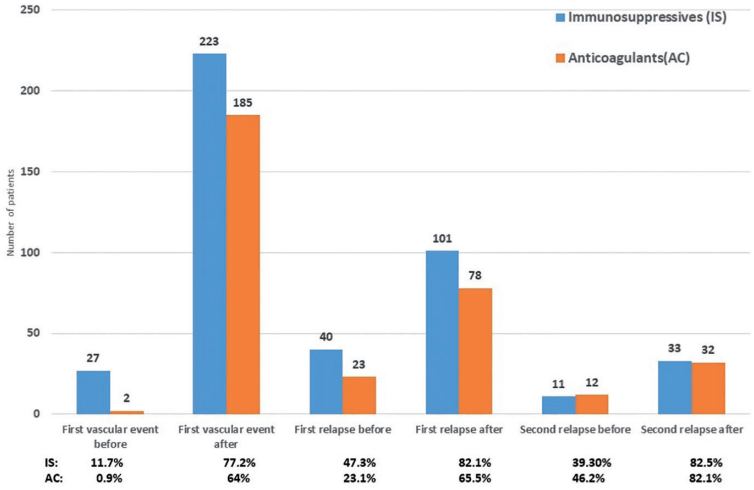

Fig. 1. Treatment of vascular events during the follow-up.

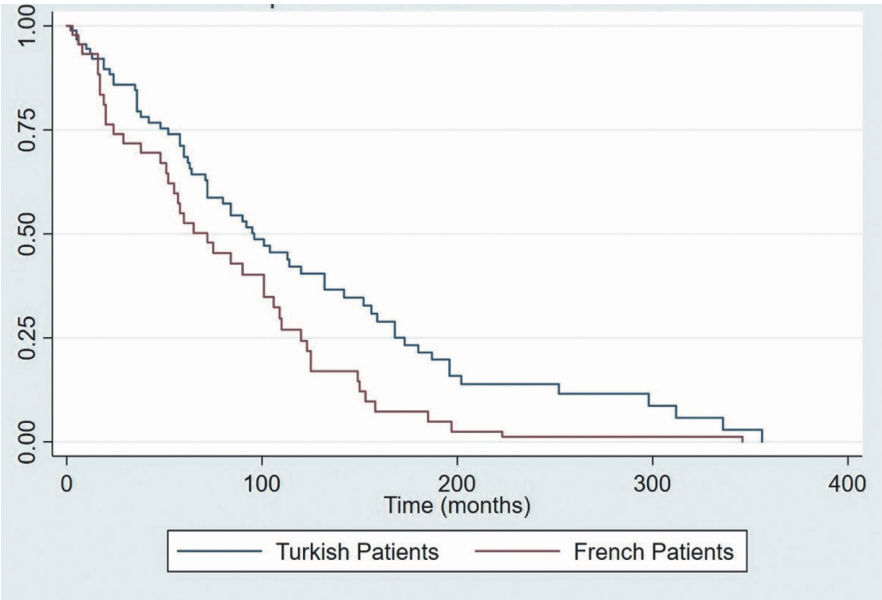

Fig. 2. Kaplan-Meier survival estimates.

tients without any treatment (p<0.05 for all comparison). But there was no difference among IS treatment groups regarding vascular relapse rate (prednisolone >10 mg: 45.2%, conventional ISs: 34.5%, TNF inhibitors: 43.8%, p>0.05). The second vascular relapse occurred in 43 (33.1%) patients after 29 (1-120) months of first vascular relapse. The third vascular relapse occurred in 37.2% (n=16) of patients after median 70.5 (5-–84) months from the second one. The relapse rate was significantly lower in patients ever using ISs between first and second relapse compared to not using ISs (25, 24.8% *vs*. 16, 72.7%, p=0.001).

Factors associated with relapses

There was no difference between patients with and without relapse regarding gender (p=0.154), age of diagnosis (p=0.140), smoking (p=0.350), family history of BD (p=0.623), first vascular involvement subtype (venous/arterial) (p=0.243) and age at first vascular event (p=0.104).

Data for IS treatment duration was available in 193 and for AC treatment in 167 patients. Median duration of anticoagulation was 24 (1–453) months and median duration of ISs was 49 (1–300) months after the first vascular event (from first vascular event until time of study). While duration of AC treatment is similar between patients with a relapse compared to patients without relapse (24 (1–364) *vs*. 18 (1–453), p=0.174), duration of IS treatment was significantly longer in patients with relapses (60 (3–300) *vs*. 36 (1–226), p<0.001). There was a weak correlation between the number of vascular events and duration of ISs (p=0.000, r=0.249), but no correlation between the number of vascular events and duration of anticoagulant usage (p=0.046, r=.154), and age at first vascular event (p=0.080, r=-0.106). We did not find any correlation between the number of vascular events and age at diagnosis (p=0.164), smoking (p=0.458) and vascular subtype (p=0.483). Relapse rate was similar between the patients with or without a positive thrombophilia factor (59.1 0% *vs*. 48.7 %, p=0.487).

Survival graph revealed that FR cohort has 1.64 times increased recurrent event risk compared to TR cohort (HR=1.64 (1.1–2.44) (p=0.014, Fig. 2) and although did not reach to statical significance, IS treatment after the first vascular event decreased further vascular events (HR= 0.66 (0.43–1.01, p=0.057).

Discussion

VBD is considered as a main cause of morbidity and mortality in BD. Relapses of DVT have been reported in one third of BD patients (4, 16). The only prospective study from Turkey showed that 45% of the 29 patients with DVT relapsed under azathioprine treatment over 40.7±13.4 months of follow-up (9). In the present study, 44.7% of patients with VBD experienced a relapse after the first vascular event during a median follow up of 24.5 months.

IS treatment is the mainstay of VBD, however there is no consensus for the duration of IS use. Median duration of IS treatment was 24 (1-189) months after the first vascular event in our study. However, the first vascular relapse developed in 34.5 (min/max: 2–276) months. A second vascular relapse has also occurred in one third (33.1%) of the patients. The median time between first and second relapse was 29 months and only 39.3% of relapsers were under any effective treatment (IS or IS+AC). These results suggest that early cessation of ISs may contribute to the high relapse rate in VBD patients during follow-up.

Due to the lack of prospective controlled studies, there is no consensus for anticoagulation for the treatment of VBD (17). In a large study of BD patients with deep vein thrombosis from France, only IS treatment significantly decreased relapse rate. Although all patients were anti-coagulated, despite a high number of associated arterial aneurysms (n=44), haemorrhagic complications were seen in only 2% (5). In another multicentre study from Turkey, the relapse rate was similar between patients using only ISs and those using anticoagulants together with ISs (29.1% *vs*. 22.4%, p=0.08) (4). In two other studies, any positive effect of anticoagulants on development of post-thrombotic syndrome after DVT was also not shown in BD (11, 18). However, we have recently shown that anti-coagulation might affect collateral development in patients with lower extremity thrombosis with post-thrombotic syndrome (19).

In the present study, relapse rate was significantly lower in patients taking only ISs compared to taking only AC (p<0.001). There was no benefit of adding ACs on IS treatment regarding relapse rate. A meta-analysis of three retrospective studies showed that ISs and anticoagulants are superior to anticoagulants alone (RR 0.17, 95% CI 0.08–0.35), and adding anticoagulants to ISs had no benefit (RR 0.75, 95% CI 0.48–1.17) in VBD. According to EULAR Recommendations, anticoagulants may be added to ISs, if the bleeding risk is thought to be low and coexistent pulmonary artery aneurysms are ruled out (13).

The prevalence of some BD manifestations can vary in different ethnic populations. GI involvement increases from west to the east with the highest frequency (up to 50%) in Japan. However, it is reported to be very rare in Mediterranean countries such as Turkey and Spain (0–5%) (20). While VBD is observed quite rare in East Asia countries such as Japan and Korea (<10%) (6, 7), it is observed in up to 40% of the patients with BD in Turkey (3-5). The pathergy test, the skin hyper-reactivity to a needle prick, was reported to be present in more than half of the BD patients among the countries such as Turkey, Japan and Mediterranean countries, whereas it is less common in northern European countries and US (21, 22).

There are very few comparative studies from different ethnic populations in BD. Cibley *et al*. compared Turkish *versus* patients from the USA and found more gastrointestinal and neurologic disease involvement in the US (23). In our study, family history for BD, HLAB*51 and pathergy positivities were significantly higher in Turkish patients whereas neurologic involvement was more prevalent in French group.

Most vascular lesions (80%) in our study affected the veins, as reported in the literature (24, 25). Pure arterial involvement was more common in TR, whereas combined vessel disease was more present in FR. Most venous disease in TR patients were in lower extremity, whereas intraabdominal disease was more common in France. Pulmonary arterial disease seems to be more present in TR patients. The reasons for these differences were not clarified, however longer follow-up of FR patients (150 *vs*. 62 months) may partially explain more severe venous disease in FR as venous disease tends to disseminate to new vascular regions when relapses are seen. However, differences in arterial disease requires further analysis.

We did not find any correlation between relapse rate and age, gender, smoking, family history of BD and vascular involvement type. The relapse rate in patients having thrombophilia factors was higher, but without reaching significance. A study from Turkey, among 96 patients with thrombosis, previously reported that VBD patients with recurrent thrombotic events had a significantly higher incidence of thrombophilia than those patients with only one thrombotic event (26). However, in our study, relapse rate was similar between VBD patients with and without thrombophilia similar to the present one.

We acknowledge limitations in our study such as the retrospective design, and the lack of effective INR monitorisation data from charts. However, large sample size and comparison in 2 different ethnic population in VBD are important strengths.

In conclusion, 44.7% of patients with VBD relapsed during follow up of median two years after first vascular event in two populations from different countries. Similar to previous studies, we did not find any additional benefit of AC treatment on relapses in VBD when used in combination with ISs. Our results suggest that early cessation of ISs and AC may contribute to higher relapse rates in VBD patients during follow-up. Randomised, controlled, prospective studies are needed to assess the contribution of AC treatment for prevention of relapses in VBD.

Take home messages

- Almost half (44.7%) of the patients with vascular Behçet's disease (VBD) relapsed during follow up of median two years after the first vascular event in two populations from different countries.
- Immunosuppressants (ISs) decrease VBD relapses.
- We did not find any additional benefit of anticoagulant treatment on relapses in VBD when used in combination with ISs.
- Our results suggest that early cessation of ISs and anticoagulants may contribute to higher relapse rates in VBD patients during follow-up.

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