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Immunosuppressants Reduce Venous Thrombosis Relapse in Behçet's Disease

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Objective. **To investigate and describe the long-term outcome of venous thrombosis in patients with Behçet's disease (BD).**

Methods. **In a retrospective cohort of 807 BD patients, a reported 296 patients (36.7%) (73.3% male, median age 30 years [interquartile range 24–36 years]) met the international classification criteria for BD and had venous thrombosis. We assessed factors associated with thrombosis relapse and mortality.**

Results. **There were a total of 586 venous thrombosis events, including 560 cases of deep thrombosis and 26 cases of superficial thrombosis. Deep venous thrombosis events included 323 cases of limb thrombosis (55.1%), 77 cases of cerebral venous thrombosis (13.1%), 57 cases of pulmonary embolism (9.7%), 63 cases of vena cava lesions (10.7%), 14 cases of Budd-Chiari syndrome (2.4%), and 13 cases of cervical vein thrombosis (2.2%). One hundred of 296 patients (33.8%) experienced at least 1 venous thrombosis relapse. The mortality rate was 6.4% (19 of 296 patients) after a median followup of 4.75 years (interquartile range 2–7 years). In univariate analysis, death was associated with cardiac involvement ($P = 0.026$) and Budd-Chiari syndrome ($P = 0.004$). In multivariate analysis, the use of immunosuppressive agents was found to prevent relapse of venous thrombosis (hazard ratio 0.27 [95% confidence interval 0.14–0.52], $P = 0.00021$), and there was a trend toward prevention of relapse with the use of glucocorticoids (hazard ratio 0.62 [95% confidence interval 0.40–0.97], $P = 0.058$).**

Conclusion. **Immunosuppressive agents significantly reduce venous thrombosis relapse in BD.**

Behçet's disease (BD) is a chronic, relapsing type of vasculitis of unknown etiology characterized by oral and urogenital ulcers and ocular inflammation with cutaneous, musculoskeletal, vascular, and nervous system manifestations (1). BD is included in the wide spectrum of vasculitis. Vasculitis is a principal pathologic finding in BD, and vessels of all sizes are involved, both in the arterial and venous systems. Large-vessel vasculitis is not a rare manifestation of BD (2,3). The prevalence of large-vessel vasculitis varies according to the findings of investigators and the populations under study.

Venous disease is more common than arterial involvement, and its reported prevalence may account for 14–39% of patients with BD (4–9). Venous thrombosis in BD is a severe disorder that may affect many different sites including the inferior vena cava, superior vena cava, pulmonary artery, suprahepatic vessels, and cardiac cavities. We previously reported that 17% of deaths in BD were caused by venous involvement, mainly pulmonary embolism or Budd-Chiari syndrome (10).

Treatment of venous thrombosis in BD is not well defined. Treatment modalities for thrombosis include glucocorticoids and other immunosuppressive agents (azathioprine, cyclosporine, cyclophosphamide), anticoagulation therapy, and intravenous thrombolysis. Interventional procedures such as filter insertion or thrombectomy have also been reported (11). However, there are no large controlled studies regarding the best approach for BD patients with thrombosis complications,

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and the exact role of anticoagulation therapy and immunosuppressive agents is still debated (12,13).

Previous studies on venous complications of BD were performed on small cohorts of patients; therefore, it was difficult to evaluate the clinical spectrum and long-term outcome of venous lesions in BD (2,3,5,6). Herein we report on the largest cohort of BD patients with venous lesions studied to date. Of 807 BD patients, 296 (36.7%) with venous thrombosis were included. We assessed the clinical spectrum, outcome, and factors associated with thrombosis relapse and mortality.

PATIENTS AND METHODS

Patients. We retrospectively studied patients with BD who were followed up in the Department of Internal Medicine of Groupe Hospitalier Pitié-Salpêtrière between 1975 and 2009. Of a cohort of 807 BD patients, 296 (36.7%) had venous thrombosis. All 296 patients met the international classification criteria for BD (14).

The diagnosis of venous thrombosis was based on data from imaging, including venous Doppler ultrasound, phlebography, cavography, computed tomography (CT) angiography, and/or magnetic resonance angiography. Cardiac cavity thrombosis was diagnosed with echocardiography.

The following data were recorded for each patient: clinical features of venous lesions (location and date of venous thrombosis), demographic characteristics (age, sex, and geographic origin), date at which BD criteria were met, number of flares, and the main associated types of BD involvement (oral and genital ulcerations and cutaneous, articular, ocular, neurologic, arterial, and cardiac manifestations). HLA–B51 typing was available for 219 of the 296 patients (74%). Ninety-three of the 296 patients (31.4%) were investigated for prothrombotic factors (protein C deficiency [normal 70–130%], protein S deficiency [normal 70–140%], and antithrombin III deficiency [normal 80–120%]); R506Q mutation of factor V Leiden, G20210A mutation of prothrombin, and C677T mutation of methylenetetrahydrofolate reductase (MTHFR) gene; plasma homocysteine level (normal 7.5–15 μmoles/liter); and anticardiolipin and anti–β_2-glycoprotein I antibodies. Anticardiolipin antibodies (aCL) were tested by enzyme-linked immunosorbent assay (normal $<$15 IU/liter). Repeated testing was systematically performed to confirm the presence of lupus anticoagulant and aCL.

Relapse was defined as a new occurrence of venous thrombosis at another site or as an extension of the initial thrombosis detected on vascular imaging. At each visit, the criteria for disease activity were applied based on symptom assessment, physical examination, and laboratory studies. Venous imaging was performed every 6–12 months, or earlier if there was uncertainty about disease progression.

Treatment strategies. Medical treatments included anticoagulants, immunosuppressive agents, and glucocorticoids. Anticoagulation consisted of heparin followed by oral anticoagulants. Anticoagulants did not include aspirin or clopidogrel. Main indications for the use of immunosuppressive agents included large-vessel thrombosis, severe cardiac lesions and/or arterial lesions, and severe uveitis and/or neurologic involvement. Immunosuppressive agents were prescribed in 53% of cases of large-vessel thrombosis, 63% of cases of neurologic involvement, 75% of cases of arterial involvement, 61% of cases of cardiac lesions, and 51% of cases of ocular involvement.

Statistical analysis. Results are expressed as the mean $\pm$ SD, the median and interquartile range (IQR), or the number (%). The association of venous involvement with patient characteristics was assessed by the Wilcoxon rank sum test for quantitative variables and by Fisher's exact test for categorical variables. Survival was defined as the time between date of diagnosis and death. Living patients were censored at the date of the last available visit. Marginal associations between single variables and survival were evaluated using a Cox model and tested by Wald's test. Hazard ratios (HRs) were provided with 95% confidence intervals (95% CIs). Cumulative incidence of venous involvement was estimated using Gray's estimator (15). Death was considered a competing event. Time to relapse was defined as the time between the date of the first venous involvement and relapse. Cumulative incidence of first relapse was estimated using Gray's estimator.

Considering that a single patient could have several relapses of disease, associations between variables and time to relapse were evaluated using a cause-specific Cox random-effects model. Variables associated with intervention at an alpha level of 0.1 were considered in a multiple model. The median followup was estimated using a Kaplan-Meier estimator considering censoring as an event. Two-sided P values less than 0.05 were considered significant. Analyses were performed using the R statistical package (online at http://www.R-project.org).

RESULTS

Characteristics of the 296 BD patients with venous involvement. Of the 807 patients with BD in our cohort, 296 (36.7%) had venous involvement, with a total of 586 venous thrombosis events. The main features of the 296 patients are summarized in Table 1.

Two hundred seventeen of the 296 patients (73.3%) were male, and the median age was 30 years (IQR 24–36 years). Most patients originated from Europe (140 of 296 [47.3%]) and North Africa (126 of 296 [42.6%]). Associated types of BD involvement included oral ulcerations (99.3%) and genital ulcerations (59.8%) and ocular (55.1%), neurologic (38.5%), articular (38.5%), arterial (18.6%), and cardiac (9.8%) manifestations. Demographic characteristics and disease manifestations were similar in patients who ever presented with venous thrombosis and those who had venous involvement at first presentation, except for lower frequencies of male sex and neurologic involvement in the latter group.

The proportion of patients with venous involvement was 21.5% (95% CI 18.2–24.7) at diagnosis (the

Table 1. Comparison of the patients with Behçet's disease according to the presence or absence of venous involvement*

	With venous involvement (n = 296)	Without venous involvement (n = 511)	*P*
Demographic features			
Male sex	217 (73.3)	317 (62)	0.0009
Age, median (IQR) years	30 (24–36)	30 (24–37)	0.91
Geographic origin			
Europe	140 (47.3)	238 (46.6)	–
North Africa	126 (42.6)	221 (43.2)	–
Africa	17 (5.7)	20 (3.9)	–
Clinical features			
Oral ulcerations	294 (99.3)	497 (97.3)	1
Genital ulcerations	177 (59.8)	309 (60.5)	1
Articular involvement	114 (38.5)	258 (50.5)	0.0006
Ocular involvement	163 (55.1)	348 (68.1)	0.0002
Cardiac involvement	29 (9.8)	18 (3.5)	0.0005
Arterial involvement	55 (18.6)	30 (5.9)	<0.0001
Neurologic involvement	114 (38.5)	144 (28.2)	0.005
HLA–B51 positive	98/219 (44.7)	211/380 (55.5)	0.014
Death	19 (6.4)	21 (4.1)	–

* Except where indicated otherwise, values are the number (%) of patients. IQR = interquartile range.

date at which international criteria for BD were met), 30.8% (95% CI 27.1–34.6) at 5 years after the diagnosis, 36.5% (95% CI 32.1–40.8) at 10 years after the diagnosis, and 40.7% (95% CI 34.8–46.6) at 20 years after the diagnosis (Figure 1). Compared to patients without venous involvement, those with venous thrombosis were more frequently male ($P = 0.0009$) and had more arterial ($P < 0.0001$), cardiac ($P = 0.0005$), and neurologic ($P = 0.005$) involvement (Table 1). Ocular involvement and articular involvement were less frequent in patients with venous involvement ($P = 0.0002$ and $P = 0.0006$, respectively).

Characteristics of venous lesions in BD. The main characteristics of venous thrombosis are summarized in Table 2. Venous lesions included 560 deep thrombosis events (95.6%) and 26 superficial thrombosis events (4.4%). Venous thrombosis included 323 cases of limb thrombosis (55.1%) (306 of the lower limb and 17 of the upper limb), 77 cases of cerebral venous thrombosis (13.1%), 57 cases of pulmonary embolism (9.7%), 44 cases of inferior vena cava thrombosis (7.5%), 19 cases of superior vena cava thrombosis (3.2%), 14 cases of Budd-Chiari syndrome (2.4%), 13 cases of cervical vein thrombosis (2.2%), 6 cases of right ventricle thrombosis (1%), and 5 cases of right atrium thrombosis (0.9%). Twenty-eight cases of thrombosis involved other vessels (retinal, ophthalmic, nasal or temporal veins, hypogastric, renal and portal veins) (Table 2).

Laboratory data. Investigations for prothrombotic factors were performed in 93 of the 296 patients with venous involvement, and prothrombotic factors were present in 42 of these 93 patients (45.2%). These mainly included MTHFR mutations (heterozygous mutations in 23 patients [54.8%] and homozygous mutations in 4 patients [9.5%]), hyperhomocysteinemia in 8 patients (19%), factor II heterozygous mutation in 5 patients (11.9%), the presence of aCL in 5 patients (11.9%), factor V Leiden heterozygous mutations in 2

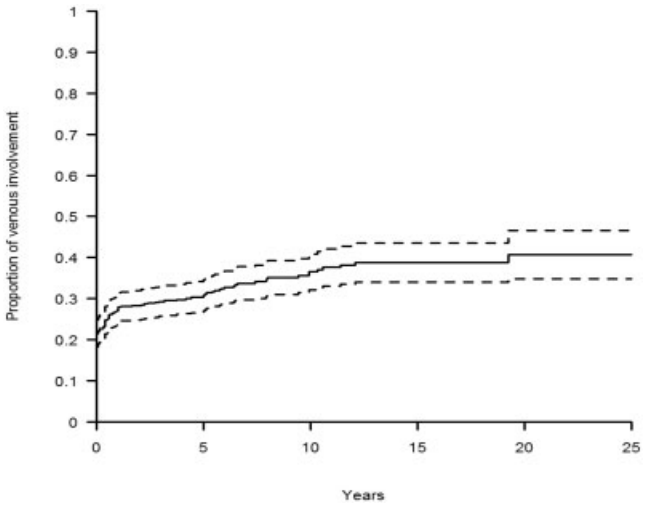

Figure 1. Cumulative incidence of venous involvement in patients with Behçet's disease, estimated using Gray's estimator (15). Median followup was estimated using the Kaplan-Meier estimator considering censoring as an event. Upper and lower broken lines represent upper and lower confidence limits, respectively.

Table 2. Characteristics of venous involvement in the BD patients*

Superficial	26 (4.4)
Deep	560 (95.6)
Multiple	207 (35.3)
Location/type of venous lesions	
Lower limbs	306 (52.2)
Cerebral veins	77 (13.1)
Pulmonary embolism	57 (9.7)
Inferior vena cava	44 (7.5)
Superior vena cava	19 (3.2)
Upper limbs	17 (2.9)
Budd-Chiari syndrome	14 (2.4)
Cervical veins	13 (2.2)
Right ventricle	6 (1)
Right atrium	5 (0.9)
Other thrombosis	28 (4.8)
Retinal	14 (0.50)
Renal	4 (0.14)
Temporal	4 (0.14)
Ophthalmic	2 (0.07)
Nasal	2 (0.07)
Hypogastric	1 (0.04)
Portal	1 (0.04)

* Values are the number (%) of events. There were 586 thrombosis events overall in the 296 patients with Behçet's disease (BD) who had venous involvement.

patients (4.8%), and protein C deficiency in 1 patient (2.4%). There were no patients with protein S or antithrombin III deficiency. HLA–B51 typing was positive in 98 of 219 patients (44.7%).

Treatment. Treatment consisted of anticoagulation in almost all patients (291 of 295 [98.6%]), as well as therapy with immunosuppressive agents (137 of 293 [46.8%]) and glucocorticoids (185 of 295 [62.7%]) (data on anticoagulation and glucocorticoid treatment missing for 1 patient, and data on immunosuppressive treatment missing for 3 patients). The median duration of anticoagulation was 10 months (IQR 4–24 months). The median duration of therapy with immunosuppressive agents was 3.1 years (IQR 1–5 years). In the 185 patients who received glucocorticoids, glucocorticoids were started at 0.5–1 mg/kg/day and then progressively tapered to <10 mg/day at 6 months. In the 137 patients who received immunosuppressive agents, 47 received cyclophosphamide (34.3%) (6 pulses of 1 gram monthly), 95 received azathioprine (69.3%) (2.5 mg/kg/day), 8 received methotrexate (5.8%), 20 received chlorambucil (14.6%), 8 received cyclosporine (5.8%), 7 received thalidomide (5.1%), 2 received infliximab (1.5%), and 4 received interferon-α (2.9%). Portosystemic shunting was performed in 3 patients with Budd-Chiari syndrome; bypass was performed for superior vena cava thrombosis

Table 3. Factors associated with death in the patients with Behçet's disease who had venous thrombosis*

	Living patients	Deceased patients	HR (95% CI)	*P*
Male sex	199 (71.8)	18 (94.74)	5.81 (0.77–43.7)	0.088
Type of thrombosis				
Lower limbs	200 (72.2)	7 (36.84)	0.19 (0.07–0.53)	0.0020
Upper limbs	17 (6.14)	0 (0.00)	–	–
Large vessels	87 (31.41)	12 (63.16)	2.52 (0.93–6.84)	0.069
Pulmonary embolism	43 (15.52)	7 (36.84)	2.09 (0.70–6.18)	0.180
Cervical veins	11 (3.97)	2 (10.53)	1.05 (0.14–8.07)	0.96
Superior vena cava	15 (5.42)	1 (5.26)	1.44 (0.19–11.06)	0.720
Inferior vena cava	37 (13.36)	6 (31.58)	1.98 (0.64–6.18)	0.240
Budd-Chiari syndrome	9 (3.25)	4 (21.05)	9.39 (2.05–43.07)	0.004
Right atrium	5 (1.81)	0 (0.00)	–	–
Right ventricle	6 (2.17)	0 (0.00)	–	–
Cerebral veins	69 (24.91)	5 (26.32)	1.18 (0.41–3.42)	0.760
Other locations	27 (9.75)	1 (5.26)	0.52 (0.07–4.02)	0.530
Associated involvement				
Articular	106 (38.27)	8 (42.11)	1.21 (0.43–3.36)	0.710
Ocular	154 (55.60)	9 (47.4)	0.51 (0.18–1.41)	0.190
Neurologic	106 (38.27)	8 (42.11)	1.03 (0.38–2.80)	0.950
Arterial	51 (18.41)	4 (21.05)	1.04 (0.30–3.65)	0.950
Cardiac	24 (8.66)	5 (26.32)	3.67 (1.17–11.55)	0.026
Oral ulcerations	275 (99.28)	19 (100.00)	–	–
Genital ulcerations	166 (59.97)	11 (57.89)	0.75 (0.27–2.04)	0.570
Relapses	94 (33.94)	6 (31.58)	–	–
Treatment				
Glucocorticoids	169 (59.93)	16 (84.21)	3.46 (0.79–15.21)	0.100
Immunosuppressive agents	123 (44.40)	14 (73.68)	2.97 (0.95–9.27)	0.061

* Values are the number (%) of patients. HR = hazard ratio; 95% CI = 95% confidence interval.

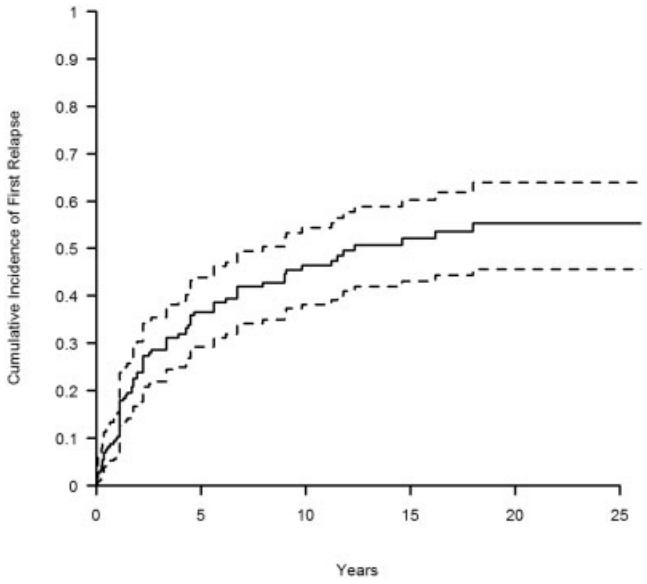

Figure 2. Cumulative incidence of first relapse of venous thrombosis in patients with Behçet's disease, estimated using Gray's estimator (15). Median followup was estimated using the Kaplan-Meier estimator considering censoring as an event. Upper and lower broken lines represent upper and lower confidence limits, respectively.

in 3 patients and thrombectomy was performed in 1 patient with renal thrombosis.

Patients with venous involvement did not receive more immunosuppressive agents than those without venous thrombosis (137 of 296 patients [46.3%] versus 299 of 511 patients [58.5%], respectively). Bleeding complications occurred in 7 patients treated with anticoagulation (2.4%). These included gastrointestinal hemorrhage (n = 2), lower limb hematoma (n = 2), subdural hematoma (n = 1), perirenal hematoma (n = 1), and hemoptysis (n = 1). There was no difference in duration or type of anticoagulation between patients with and those without bleeding complications.

Factors associated with mortality. Data on mortality are summarized in Table 3. The mortality rate was 6.4% (19 of 296 patients with venous thrombosis) after a median followup of 4.75 years (IQR 2–7 years). The mortality rate tended to be higher in BD patients with venous thrombosis than in those without (4.1%).

The causes of death included Budd-Chiari syndrome (n = 4 [21.1%]), neurologic involvement (n = 4 [21.1%]), cardiovascular involvement (n = 4 [21.1%]) (2 ruptured aneurysms, 1 endocarditis, and 1 myocardial infarction), pulmonary embolism (n = 3 [15.8%]), sepsis (n = 2 [10.5%]), cancer (n = 1), and unknown etiology (n = 1). In univariate analysis, death was associated with cardiac involvement ($P = 0.026$) and Budd-Chiari syndrome ($P = 0.004$) (Table 3). Deaths were significantly

Table 4. Factors associated with venous thrombosis relapse*

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	0.99 (0.97–1.01)	0.30	–	–
Location/type of thrombosis				
Upper limb veins	0.96 (0.35–2.6)	0.94	–	–
Lower limb veins	1.28 (0.86–1.92)	0.23	–	–
Pulmonary embolism	0.93 (0.56–1.56)	0.79	–	–
Cerebral veins	1 (0.58–1.73)	0.99	–	–
Cervical veins	0.91 (0.33–2.45)	0.84	–	–
Superior vena cava	0.97 (0.43–2.2)	0.94	–	–
Inferior vena cava	0.6 (0.31–1.15)	0.12	–	–
Budd-Chiari syndrome	1.52 (0.37–6.21)	0.56	–	–
Right atrium	1.34 (0.19–9.59)	0.77	–	–
Right ventricle	0.62 (0.09–4.44)	0.63	–	–
Other locations	0.37 (0.12–1.15)	0.086	–	–
Associated involvement				
Oral ulcerations	0.27 (0.04–1.94)	0.19	–	–
Genital ulcerations	1.12 (0.79–1.6)	0.52	–	–
Articular	1.05 (0.74–1.49)	0.78	–	–
Ocular	0.82 (0.58–1.15)	0.24	–	–
Neurologic	1.52 (1.07–2.14)	0.018	2.07 (1.36–3.15)	0.0028
Arterial	1.06 (0.69–1.62)	0.79	–	–
Cardiac	0.72 (0.35–1.47)	0.36	–	–
Treatment				
Glucocorticoids	0.71 (0.47–1.07)	0.099	0.62 (0.40–0.97)	0.058
Immunosuppressive agents	0.26 (0.14–0.49)	<0.0001	0.27 (0.14–0.52)	0.00021

* HR = hazard ratio; 95% CI = 95% confidence interval.

less frequent in patients with thrombosis of the lower limbs ($P = 0.002$) (Table 3).

Factors associated with venous thrombosis relapse. The incidence of first relapse was 36.5% (95% CI 29.2–44.8) at 5 years, 46.4% (95% CI 38.1–54.3) at 10 years, and 55.3% (95% CI 45.6–63.9) at 20 years after thrombosis (Figure 2). One hundred of 296 patients (33.8%) experienced at least 1 relapse of venous thrombosis. Venous thrombosis relapse included deep vein thrombosis of the lower limbs (n = 116 [57.7%]) or upper limbs (n = 6 [3%]), pulmonary embolism (n = 21 [10.4%]), inferior vena cava (n = 16 [8%]), cervical veins (n = 5 [2.5%]), Budd-Chiari syndrome (n = 5 [2.5%]), superior vena cava (n = 4 [2%]), bypass thrombosis (n = 4 [2%]), right atrium (n = 3 [1.5%]), cerebral venous thrombosis (n = 17 [8.5%]), and other locations (n = 4 [2%]).

Relapses of thrombosis occurred in 8 patients treated with immunosuppressive agents (20%) compared to 68 not treated with immunosuppressive agents (56%). The frequency of prothrombotic factors in patients who had a venous thrombosis relapse was similar to that in the whole cohort (46.5% and 45%, respectively).

In univariate analysis (Table 4), factors that prevented venous thrombosis relapse were the use of immunosuppressive agents (HR 0.26 [95% CI 0.14–0.49], $P < 0.0001$) and the use of glucocorticoids (HR 0.71 [95% CI 0.47–1.07], $P = 0.099$). The factor significantly associated with the occurrence of venous thrombosis relapse was the presence of neurologic involvement (HR 1.52 [95% CI 1.07–2.14], $P = 0.018$).

In multivariate analysis (Table 4), the use of immunosuppressive agents was found to prevent relapse of venous thrombosis (HR 0.27 [95% CI 0.14–0.52], $P = 0.00021$), and there was a trend toward prevention of relapse with the use of glucocorticoids (HR 0.62 [95% CI 0.40–0.97], $P = 0.058$). The presence of neurologic involvement was again significantly associated with the occurrence of venous thrombosis relapse (HR 2.07 [95% CI 1.36–3.15], $P = 0.0028$).

DISCUSSION

Our experience is derived from the largest cohort of BD patients with venous involvement studied to date. The most important conclusions that we can draw from this study are that immunosuppressive agents improve prognosis by decreasing the odds of venous thrombosis relapse in BD by 4-fold, and that Budd-Chiari syndrome is the most severe type of venous involvement in BD, increasing the risk of death by 9-fold.

Consistent with previous studies (4–9), the prevalence of venous thrombosis in our series was 36.7%. We found deep vein thrombosis in 95.6% of patients, with 52.2% of venous lesions located in the lower limbs. Large-vessel involvement (i.e., thrombosis of the inferior and/or superior vena cava, cerebral veins, cervical veins, pulmonary embolism, cardiac cavities, and Budd-Chiari syndrome) accounted for 40% of thrombosis cases in our BD patients.

The pathogenesis of thrombosis in BD is not fully understood. It is unlikely that thrombophilia plays a role in the thrombosis pathogenesis in most patients with BD, since no consistent primary abnormality of the coagulation or fibrinolytic system has yet been identified (16,17). As the likely cause of deep vein thrombosis in BD patients is venous inflammation, an immunosuppression approach to management is quite reasonable, although there are no large randomized controlled trials directly addressing this issue. Strikingly, immunosuppressive agents significantly improved the prognosis in our study, decreasing the likelihood of thrombosis relapse by 4-fold. A retrospective study of 37 patients with venous thrombosis in BD compared immunosuppressive agents, anticoagulation treatment, and the combination of immunosuppressive agents and anticoagulation treatment (18). Three of the 4 patients in the anticoagulant-treated group (75%) developed new thromboses, compared to 2 of 16 patients in the immunosuppressive agent–treated group (12.5%) and 1 of 17 patients in the combination-treated group (5.9%). Our study was not designed to address whether immunosuppressive agents were beneficial in all cases of deep vein thrombosis in BD (i.e., in lower limbs as well as in large vessels).

Regarding anticoagulation, there are neither controlled data nor evidence of benefit from uncontrolled studies of anticoagulants in the management of deep vein thrombosis in BD. Some authors recommend anticoagulants for major vein thrombosis, while others suggest that they be avoided owing to the increased risk of fatal bleeding from coexisting pulmonary arterial aneurysm, and owing to the estimated low risk of pulmonary embolism in BD. In our study, almost all BD patients with deep vein thrombosis received anticoagulation therapy despite a high number of associated arterial aneurysms (n = 44 [14.9%]), 8 of which were pulmonary arterial aneurysms. The tolerance was satisfactory, with only 2% of patients having hemorrhagic complications. On the other hand, pulmonary embolism accounted for 10% of all cases of thrombosis and 15.8% of deaths.

Seventy percent of our BD patients with pulmonary embolism presented with concomitant lower limb thrombosis. Distinguishing between in situ thrombosis and pulmonary embolism may be challenging. Regardless of the presence of deep venous thrombosis, the pulmonary artery thrombi may originate in situ, secondary to pulmonary artery wall inflammation. On CT images a rim of enhancement at the filling defects may be depicted; this finding is consistent with inflammation —a finding that is not usually seen in acute or chronic pulmonary embolism. Consistent with our results, Mehta et al (19) reported a prevalence of pulmonary embolism of 27.4%. Although 89% of patients in their study were being treated with anticoagulants, bleeding complications were only noted in 2 cases.

The mortality rate tended to be higher in BD patients with venous involvement than in those without. Strikingly, in patients with large-vessel thrombosis, the mortality rate reached 12.1%. Consistent with the findings of previous studies (10,20), the rate of mortality was higher in males and in patients with cardiac involvement. Lower limb vein thrombosis was associated with a favorable outcome. In contrast, Budd-Chiari syndrome was the most severe venous involvement in BD, increasing the odds of death by 9-fold. Immunosuppressive agents were not associated with decreased mortality. This might be explained by the fact that patients who died were most likely those who were treated with immunosuppressive agents for life-threatening manifestations of BD. Hepatic vein thrombosis was reported in 26.4% of a series of 53 BD patients with large-vessel thrombosis (21). In another study (22), 21 cases of hepatic vein thrombosis caused by BD (4 reported by the authors and 17 from the literature) were compared to 24 cases of hepatic vein thrombosis caused by primary myeloproliferative disorders. Five of 20 patients with BD had acute liver failure and died within the first month of clinical onset, while patients with myeloproliferative diseases had a progressive course. Most patients remain at risk for slowly progressive liver failure, elevated portal pressure, and esophageal varices.

We acknowledge some limitations in our study. The analysis was performed as a retrospective review. We were unable to collect complete longitudinal data on patients who were seen only on an intermittent consultation basis. Prospective enrollment and data collection from the time of diagnosis would be ideal but is more difficult to achieve in studies of rare diseases.

In conclusion, Budd-Chiari syndrome was the most severe venous involvement in our cohort of BD patients. Immunosuppressive agents significantly reduced the incidence of venous thrombosis relapse in the BD patients. The tolerance of anticoagulation therapy was satisfactory, with hemorrhagic complications in 2% of patients. Further studies are warranted to determine the role of anticoagulation therapy in BD patients with venous thrombosis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saadoun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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