



## **Adalimumab-Based Treatment Versus Disease-Modifying Antirheumatic Drugs for Venous Thrombosis in Behçet's Syndrome: A Retrospective Study of Seventy Patients With Vascular Involvement**

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## **Adalimumab-based treatment versus DMARDs for venous thrombosis in Behçet syndrome. A retrospective study of 70 patients with vascular involvement.**

**Running title:** Adalimumab vs DMARDs in Behçet-induced thrombosis

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**Conflict of interest:** None

## **Abstract**

**Objectives** Since Behçet syndrome (BS) is the prototype of inflammation-induced thrombosis, immunosuppressants are recommended in place of anticoagulants. Here we assessed the clinical efficacy and the corticosteroid-sparing effect of adalimumab (ADA)-based treatment versus DMARDs in a large retrospective cohort of patients with BS-related venous thrombosis.

**Methods** We retrospectively collected data from 70 BS patients treated with DMARDs or ADA-based regimens (ADA ± DMARDs) because of venous complications. Clinical and imaging evaluations were performed to define vascular response. We explored differences in outcomes between ADA-based regimens and DMARDs, with respect to efficacy, corticosteroid-sparing role and time on treatment. We also evaluated the role of anticoagulants as concomitant treatment.

**Results** After a mean follow-up of 25.7±23.2 months, ADA-based regimens induced clinical and instrumental improvement of venous thrombosis more frequently ( $p=0.001$ ) and rapidly ( $p<0.0001$ ) than DMARDs. The mean dose of corticosteroids administered at the last follow-up was significantly lower in the ADA-based regimens than in the DMARDs one ( $p<0.0001$ ). The time on treatment was significantly longer in ADA-based regimens than in the DMARDs one ( $p=0.002$ ). No differences were found in terms of efficacy and time on treatment between DMARDs or ADA-based regimens among subjects receiving anticoagulants and those who did not.

**Conclusions** In this large retrospective study we have shown that ADA-based regimen is more effective and rapid in inducing resolution of venous thrombosis in BS patients than DMARDs, allowing reduction of steroid exposure. Moreover, our findings suggest that anticoagulation does not modify the efficacy on venous complications of either ADA-based regimens or DMARDs.

**Keywords:** Behçet's syndrome; angio-Behçet; venous thrombosis; anti-TNF $\alpha$  agents; adalimumab.

## Introduction

Behçet syndrome (BS) is a systemic vasculitis characterised by protean manifestations, such as mucocutaneous and ocular lesions, but also articular, neurological, gastrointestinal and vascular involvement<sup>1</sup>. Vascular manifestations occur in up to 50% of patients and affect both venous and arterial vessels of variable size; deep vein thrombosis (DVT) and recurrent superficial vein thrombophlebitis (SVT) of lower extremities are the most common vascular manifestations of the disease. Venous thrombosis occurs more frequently during active disease in male subjects and tends to recur, making it one of the most important causes of morbidity and mortality in BS patients<sup>2</sup>. Systemic inflammation seems to be the main trigger of thrombosis. Although the pathogenic mechanisms of BS-related thrombosis are still incompletely understood, we have recently demonstrated that neutrophils are able to induce deep modifications in fibrinogen structure, which becomes more resistant to plasmin<sup>3</sup>. These data support the European League Against Rheumatism (EULAR) recommendations for the management of thrombosis in BS patients, which suggest the use of immunosuppressants as Disease Modifying Antirheumatic Drugs (DMARDs) rather than oral anticoagulation as first-line therapy<sup>4,5</sup>. Recently, several reports have shown the efficacy of anti-tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) agents for BS-related vascular complications<sup>6-9</sup>, especially for patients with arterial involvement<sup>10</sup>. However, there are neither prospective controlled trials nor large retrospective studies focussing on the treatment of deep and/or superficial vein thrombosis in BS patients.

In the present study, we evaluated the clinical efficacy and the corticosteroid-sparing effect of adalimumab (ADA)-based regimens versus DMARDs alone in a large retrospective cohort of patients with BS-related venous thrombosis.

## Patients and Methods

We retrospectively collected clinical data from patients diagnosed with BS and treated with DMARDs as the sole immunosuppressive therapy or ADA-based regimens (ADA combined or not with DMARDs) because of recurrent venous vascular manifestations. All patients were seen at the Behçet Centre of the University Hospital of Florence between January 2009 and January 2017. The diagnosis of BS was based on the International Criteria for Behçet's disease (ICBD)<sup>11</sup>. Venous involvement included DVT and SVT of the lower and upper limbs; SVT and DVT were defined as recurrent if they occurred at least twice during patient observation. Patients with BS-related arterial involvement and/or venous disease affecting sites other than lower and upper limbs were excluded from the study (*figure 1*).

As per our clinical practice, patients with venous events were clinically and sonographically evaluated every four weeks for the first three months after the event, and then every three months or in case of BS relapse; all ultrasounds were performed by the same trained vascular ultrasound specialist (M.B.). DVT and SVT were diagnosed by bilateral compression of upper or lower limb ultrasound. Diagnostic criteria were cross sectional vein incompressibility, direct thrombus imaging with vein enlargement, and abnormal spectral and color-Doppler flow<sup>12</sup>. The Doppler ultrasound response was defined as follows: a) complete resolution of venous thrombosis; b) partial response with revascularisation, characterised by the presence of non-haemodynamically relevant parietal thrombosis; c) no response or thrombosis progression. Clinical response was defined as the disappearance of signs and symptoms related to DVT and/or SVT. A complete response was defined as a both clinical and instrumental resolution of thrombosis; a partial response was represented by a clinical resolution plus a partial instrumental response or no progression of thrombosis; no response was defined as the absence of both clinical and instrumental response. Globally, both complete and partial response has been defined in the text as “vascular response”. The

occurrence of post-thrombotic syndrome was not considered in the evaluation of vascular outcome.

The collected data included the age at BS onset, HLA-B51 positivity, clinical manifestations occurred at any time since disease onset, and all available information regarding treatment (time at ADA-based regimen or DMARD initiation, concomitant therapies, corticosteroid dosages at the start of treatment and at last follow-up or at disease relapse). We also assessed the clinical and imaging response to different treatments, the time required to achieve clinical response, the occurrence of vascular relapses during treatments, the time elapsed between the start of DMARDs or ADA-based treatment and vascular relapse, and any oral anticoagulant treatment associated with ADA-based regimens or DMARDs.

Specific aims of this study were: i) to explore differences in the efficacy on SVT and DVT between ADA-based regimens and DMARDs alone, focusing on response rates and time to vascular response; ii) to compare the corticosteroid-sparing role of ADA-based regimens *versus* DMARDs alone; iii) to compare the time on treatment of ADA-based regimens and DMARDs alone; iv) to evaluate the role of concomitant anticoagulant therapy on vascular responses in patients treated with ADA-based regimens or DMARDs alone.

The Graphpad Prism 6.0 software was used for statistical computation. Continuous variables are reported as mean  $\pm$  standard deviation or median (range) as appropriate, and categorical variables as n (%). For pairwise comparisons, the Mann-Whitney U test was employed for continuous variables after having determined their non-Gaussian distribution with Anderson–Darling test; Fisher exact test was employed for categorical variables. We analysed the time on treatment, defined as the time elapsed between the start of the therapy (for venous complications) and the discontinuation of treatment or last follow-up, by using the Kaplan–

Meier method. Statistical differences in the survival rates were assessed using the log-rank test (Mantel-Cox). P values <0.05 were considered statistically significant.

The study was approved by the Ethics Committee of Careggi Hospital. All patients gave their informed consent for collection and publication of data and the study was conducted in accordance with the declaration of Helsinki.

## Results

Of the 275 patients with BS seen at our Centre during the study period, 78 had suffered from DVT and/or SVT of the upper or lower limbs. Eight of them were excluded from this study because they had been treated with anti-TNF $\alpha$  agents other than ADA. The remaining 70 (37 men, 33 women) were included in the study (*figure 1*). Among the enrolled patients, 35 (18 men, 17 women) had been treated with DMARDs alone and 35 (19 men, 16 women) with ADA-based regimens (ADA alone or combined with DMARDs). *Table 1* summarises the demographic and clinical features of the 70 patients enrolled. Of the 35 patients who received DMARDs, 18 (51%) were treated with azathioprine, nine (26%) with cyclosporine, five (14%) with cyclophosphamide and three (9%) with methotrexate. Of the 35 patients treated with ADA, 27 received ADA-monotherapy and 8 ADA plus DMARDs (azathioprine in seven patients and methotrexate in one). Apart from severe oral aphthosis, 10/35 patients treated with DMARDs alone and 16/35 treated with ADA-based regimens suffered from vascular involvement as the sole disease manifestation at the start of therapy (*table 1*).

During a mean follow-up of  $25.7\pm 23.2$  months, ADA-based regimens and DMARDs were able to induce vascular responses in 34/35 patients (97.1%) and 23/35 patients (65.7%), respectively. The frequency of complete or partial vascular responses was significantly higher among patients treated with ADA-based regimens ( $p=0.001$ ).

With regards to the patients who initially presented with SVT only, vascular responses were observed in 3/4 cases (75%) treated with ADA-based regimens and in 3/7 cases (42.86%) treated with DMARDs ( $p=0.545$ ). ADA-based regimens were used in the patients with SVT given the presence of other disease manifestations (two had ocular involvement, one severe oral aphthosis and erythema nodosum, and one oral aphthosis and arthritis).

Among patients with initial DVT (17 treated with ADA-based regimens and 12 with DMARDs), ADA-based regimens induced a significantly higher vascular response rate than did DMARDs (76.47 vs 33.33%;  $p=0.029$ ).

The mean time required to achieve a vascular response (either complete or partial) was  $3.7\pm 1.7$  weeks for ADA-based regimens and  $6.3\pm 1.2$  weeks for DMARDs. The time to response was significantly shorter for the ADA-based regimens than the DMARDs group (log-rank test  $p<0.0001$ ).

The mean dose of corticosteroids administered at the start of therapy was  $23.1\pm 13.1$  mg/day of prednisone (or equivalent) among patients treated with ADA-based regimens and  $26.2\pm 20.2$  mg/day of prednisone (or equivalent) among subjects treated with DMARDs alone ( $p=0.96$ ). The mean dose of prednisone (or equivalent) administered at last follow-up visit was  $3.6\pm 3.4$  mg/day in the ADA-based regimens and  $8.3\pm 3.7$  mg/day in the DMARDs group ( $p<0.0001$ ). The mean decrease in prednisone dose was  $20.4\pm 13.1$  mg/day for patients treated with ADA-based regimens and  $17.7\pm 20.3$  mg/day for patients given DMARDs ( $p=0.20$ ).



The mean prednisone dose administered at last follow-up for isolated vascular involvement was  $4.3\pm 3.8$  in patients treated with ADA-based regimens and  $10.2\pm 4.6$  mg/day for patients in the DMARDs group ( $p=0.002$ ); the mean prednisone reduction for isolated vascular involvement was  $20.0\pm 15.4$  vs  $19.1\pm 17.2$  mg/day ( $p=0.908$ ) in the ADA and DMARD groups, respectively.

When we evaluated the time on treatment, we observed that it was significantly longer in the ADA-treated patients than in those treated with DMARDs alone (log-rank test  $p=0.001$ ) (*figure 2A*). Additionally, the time on treatment was significantly longer in subjects who received ADA plus DMARDs than in those who received DMARDs alone (log-rank test  $p=0.002$ ). Likewise, it was longer in those treated with ADA alone than in those treated with DMARDs alone, although this last difference was only of borderline statistical significance (log-rank test  $p=0.051$ ) (*figure 2B*).

The time on treatment for ADA-based regimens and DMARDs alone was independent of the presence of organ manifestations other than vascular involvement (data not shown). Among patients treated with ADA-based regimens, there was no statistically significant difference in the time on treatment between those having vascular involvement as the sole disease manifestation at the start of therapy (apart from oral aphthosis) and those having other disease manifestations (log-rank test  $p=0.36$ ) (*figure 2C*). A comparable time on treatment was also observed in DMARDs-treated patients with or without other disease manifestations (log-rank test  $p=0.83$ ) (*figure 2D*).

During the follow-up, 9/35 patients (25.7%) discontinued ADA due to lack of efficacy (1 patient), loss of efficacy on vascular and extravascular manifestations (3 and 3 patients, respectively), and the occurrence of generalised urticarial skin rash after ADA injection (2 cases).

With regards to the 3 subjects with vascular relapse who had originally responded to ADA, one with initial stroke had a new stroke, one with initial bilateral SVT had a recurrence of bilateral SVT, and another with initial bilateral SVT and unilateral DVT experienced a new unilateral DVT.

Among patients treated with DMARDs, 27/35 (77.1%) switched to other therapies because of lack of efficacy (6 patients), loss of efficacy (17 patients, 14 of which for vascular relapses), adverse events (2 patient), loss of adherence (2 cases).

Among the 14 subjects with vascular relapse after DMARD therapy, five with initial DVT had a new DVT, 2 with initial SVT re-experienced SVT, and one with initial DVT developed SVT; the remaining six patients, who presented with both SVT and DVT at diagnosis, had either a new SVT (3 cases), a new DVT (1 case), or both SVT and DVT (2 cases).

The proportion of patients discontinuing the therapy because of loss of efficacy over time was significantly higher among patients treated with DMARDs ( $p=0.01$ ).

The mean time to vascular relapse was  $29.9\pm 24.4$  months for patients treated with DMARDs and  $33.7\pm 9.1$  months for patients treated with ADA-based regimens.

We also assessed the role of concomitant anticoagulant therapy on vascular responses: warfarin therapy was concomitantly given to 11/35 patients treated with ADA-based regimens (of whom 7 with DVT and 4 with both DVT and SVT), and 10/35 patients treated

with DMARDs (of whom 1 with recurrent SVT, 1 with DVT, and 8 with both DVT and SVT) ( $p=0.44$ ).

No differences were found in the frequency of response to DMARDs ( $p=0.26$ ) or ADA-based regimens ( $p=0.31$ ) between subjects who were receiving anticoagulants and those who were not (*figure 3*). Also the time on ADA-based regimens or DMARDs alone did not statistically differ between patients who did or did not receive anticoagulants ( $p=0.78$  and  $p=0.40$ , respectively) (*figure 4*).

In relation to the safety profile, one case of Herpes Zoster virus reactivation and one case of pneumonia were recorded among patients treated with ADA-based regimens, along with the 2 aforementioned cases of generalised skin rash.

## Discussion

Vascular involvement in BS represents a clinical issue in terms of morbidity and mortality<sup>13</sup> and the optimal clinical management still remains a matter of debate<sup>14,15</sup>. Anti-TNF $\alpha$  agents are increasingly reported as the treatment of choice for different organ involvements in BS<sup>5,16,17,18,19,20</sup>; nevertheless, only few data are available on the role of TNF $\alpha$  inhibition in BS patients with vascular involvement<sup>10,21</sup>.

To the best of our knowledge, our study represents the largest experience on the use of TNF $\alpha$  blockers for typical BS-related venous thrombosis. Indeed, although venous thromboses (both DVT and recurrent SVT) are the most frequent vascular manifestations in BS<sup>13,22,23</sup>, the role of TNF $\alpha$  inhibitors is mainly reported in patients with arterial complications<sup>10</sup>, especially those involving pulmonary vessels<sup>24,25,26</sup>. In contrast, infliximab has been described as poorly

effective in patients with atypical venous involvement (Budd-Chiari syndrome)<sup>21</sup>, whereas its efficacy on DVT of the lower limbs has been only anecdotally reported<sup>27</sup>.

Our retrospective evaluation shows that an ADA-based regimen is a valuable choice for the treatment of venous manifestations, and that it achieves better results than DMARDs alone. In particular, when DVT and/or SVT were present at the start of treatment, ADA-based regimens induced vascular response in a significantly greater proportion of patients than did DMARDs. Moreover, ADA-based regimens induced a more rapid resolution of the vascular manifestations as compared with DMARDs. Consequently, as venous thrombosis requires an early treatment able to induce a quick response, TNF $\alpha$  inhibition may represent an optimal therapy in this clinical setting.

Anti-TNF $\alpha$  agents have already been described as having a corticosteroid-sparing effect in BS patients<sup>9,28</sup>, but specific data on subjects with vascular manifestations are lacking. In this regard, although in our study no significant differences were found in the mean corticosteroid dosage between patients treated with ADA and those administered with DMARDs at the start of treatments, steroid dosage was significantly lower among subjects treated with ADA at the last follow-up visit. As also supported by the faster action of ADA-based regimens, our data suggest that patients treated with ADA are overall less exposed to systemic corticosteroids than patients given DMARDs alone. This may allow a lower rate of glucocorticoids-induced side effects in BS patients.

In our work, the proportion of patients discontinuing the treatment due to loss of efficacy over time was significantly higher in the DMARDs than in the ADA-based regimens. Moreover, patients on ADA-based regimens remained on treatment for a longer period of time as compared with those given DMARDs alone, with more than 50% of patients on ADA-based regimens still on treatment after 80 months. Intriguingly, the time on treatment was significantly longer in patients on combination therapy (ADA plus DMARDs) than in those on DMARDs alone. Similarly, the time on ADA-monotherapy tended to be higher than in patients on DMARDs monotherapy. These data parallel those previously reported in other chronic inflammatory conditions, such as rheumatoid arthritis<sup>29</sup>. Of note, no differences were found in terms of time on treatment when the analysis was stratified according to the presence or absence of manifestations other than vascular involvement at the start of therapies. This finding is of some interest for clinicians, since -apart from classic manifestations such as oral and genital aphthous/ulcerative lesions- the clinical phenotypes of BS are extremely diverse<sup>30</sup>. Nevertheless, the therapeutic outcome does not seem to be influenced by concurrent disease manifestations in patients with vascular involvement.

An interesting result of our study relates to the role of oral anticoagulation for the treatment of BS-related venous complications. This topic is one of the most debated among BS specialists, and clear and definite data on the real role of oral anticoagulation are lacking. In particular, the EULAR recommendations do not suggest the use of anticoagulants as first-line treatment, and recent retrospective studies have shown that the risk of DVT is lower in patients treated with immunosuppressive agents than in those only receiving anticoagulants<sup>31,32,33</sup>. On the other hand, as recently pointed out by Seyahi and Yazici<sup>34</sup>, the role of anticoagulation in BS patients might be still of some help in non endemic areas where it is more difficult for clinicians not familiar with BS to correctly attribute vascular manifestations to BS itself.

In this context, in our patients anticoagulation did neither influence the response rate nor the time on treatment of both ADA-based and DMARDs therapies. Nevertheless, these results should be taken with caution, as the lack of statistically significant differences in outcomes between patients with and those without anticoagulation may be related to the limited size of study cohort.

In the present study, adverse events were rare in both groups, thus confirming the good safety profile of ADA in the treatment of BS<sup>35</sup>.

Our study has some limitations, mainly related to its retrospective nature. In addition, in our study we only included patients with “typical” venous events such as DVT and SVT involving the upper and lower limbs. Indeed, the objective response of some “atypical” venous events (e.g suprahepatic thrombosis, vena cava thrombosis or cerebral vein thrombosis) is more difficult to objectively assess, thus inducing to exclude these kinds of vascular involvement. On the other side, arterial involvement needs a different follow-up strategy<sup>4</sup>. However, some strengths deserve to be underlined: this is the largest study that investigated the efficacy of ADA-based regimens compared to DMARDs alone on venous thrombosis, and it is the only one considering a homogenous vascular involvement (DVT and/or SVT of lower and upper limbs). These data shed some lights on one of the major complications of BS, indirectly confirming our previous experimental data on the inflammatory nature of venous thrombosis in this condition<sup>3</sup>. Indeed, vascular involvement in BS represents a unique example of inflammation-induced thrombosis; experimental data<sup>3</sup>, previous clinical experience<sup>4</sup> and our own findings suggest the use of immunosuppressants for vascular involvement in BS.

In conclusion, to date this is the largest study to evaluate the role of TNF $\alpha$ -blockers in vascular BS, and to provide strong evidence in support of their use for the treatment of venous thrombosis. In particular, we have shown that ADA-based regimens are more

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effective and rapid in inducing the resolution of venous involvement in BS patients when compared to DMARDs used as monotherapy. Their prompt effect allowed the minimisation of exposure to corticosteroids. Moreover, our findings support the notion that anticoagulation does not modify the efficacy of either ADA-based regimens or DMARDs, thus strengthening the view that inflammation rather than thrombophilic factors play a role in the pathogenesis of vascular complications in BS. Prospective controlled studies are warranted to corroborate our findings.

**Author Contributions:** All the authors were involved in drafting the article, read and approved the final version of the article. Giacomo Emmi had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. Study conception and design: GE, AV, AV, LC. Acquisition of data: GE, AV, ES, MB, CF, CF, BF, LE, GDS, MG. Ultrasound performing: MB. Analysis and interpretation of data: GE, AV, AB, AV, LC, DP.

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## Figure Legend

**Figure 1** Study flow diagram.

**Figure 2** Overall time on treatment assessed with the Kaplan-Meier method in the following groups: A) patients on Adalimumab (ADA)-based regimens and patients treated with disease modifying anti-rheumatic drugs (DMARDs) alone; B) patients treated with DMARDs alone, ADA as monotherapy and those co-administered with ADA *plus* DMARDs. The asterisk indicates the log rank *p*-value relative to the comparison ADA *plus* DMARDs versus DMARDs alone; the hashtag indicates the log rank *p*-value computed between patients treated with ADA as monotherapy and those administered with DMARDs alone; C) retention rate of ADA-based regimens differentiating between patients suffering from Behçet's syndrome (BS)-related vascular involvement as the sole clinical manifestation at the start of ADA treatment (baseline) and those complaining from other additional BS manifestations at the start of treatment; D) retention rate of DMARDs differentiating patients presenting with BS-related vascular involvement as the sole clinical manifestation at the start of treatment (baseline) and those complaining from additional other BS manifestations at the start of treatment.

**Figure 3** Frequency of responsiveness to Adalimumab (ADA)-based regimens and disease modifying anti-rheumatic drugs (DMARDs) alone, differentiating patients according to the concomitant use of anticoagulants. *P*-values have been obtained by Fisher exact test and refer to the frequency of efficacy (complete *plus* partial response) of ADA-based regimens ( $p=0.31$ ) and DMARDs ( $p=0.26$ ) in patients administered or not with concomitant anticoagulants.

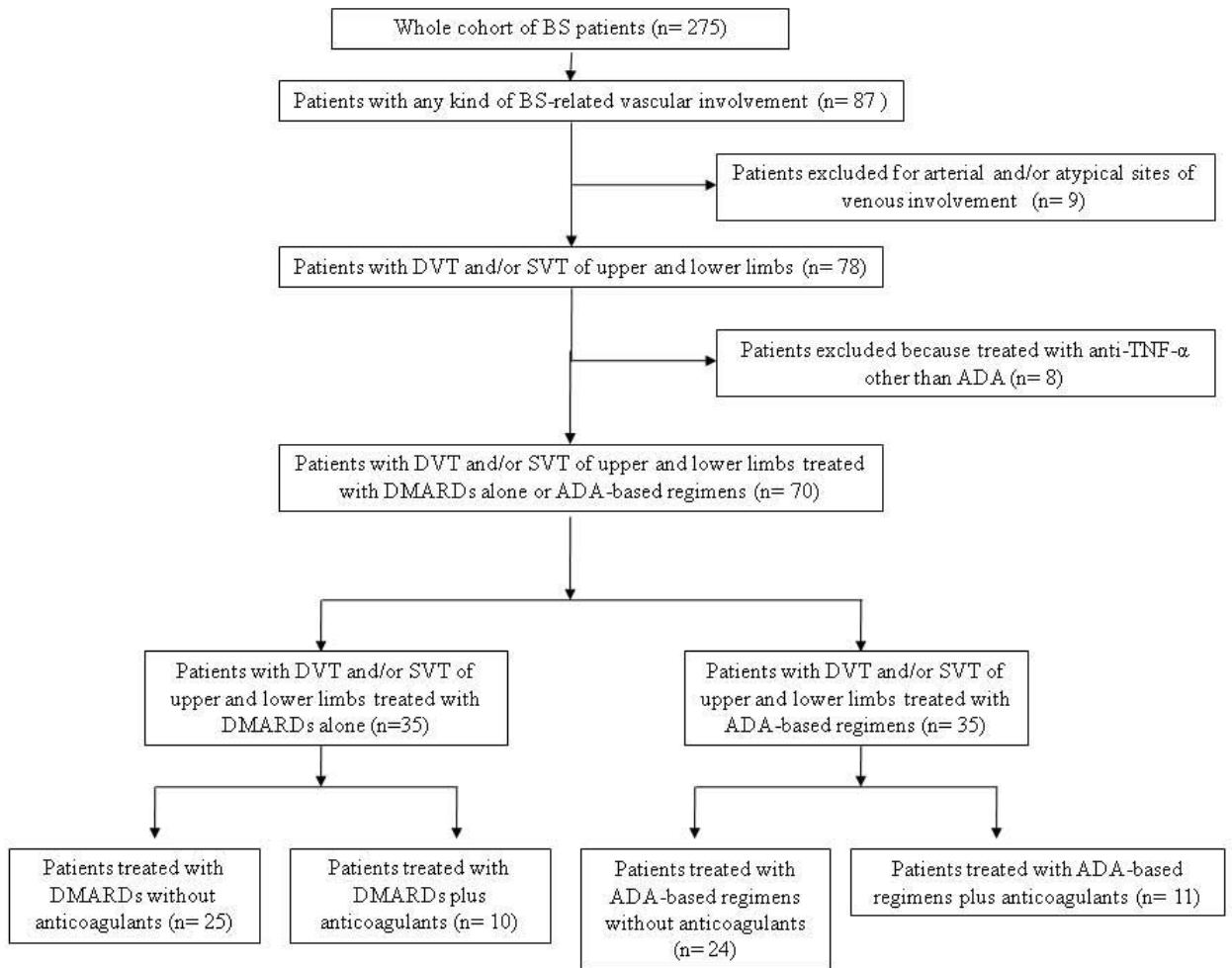
**Figure 4** Survival rates of ADA-based regimen (A) and DMARDs alone (B) differentiating patients according to the concomitant use of anticoagulants.

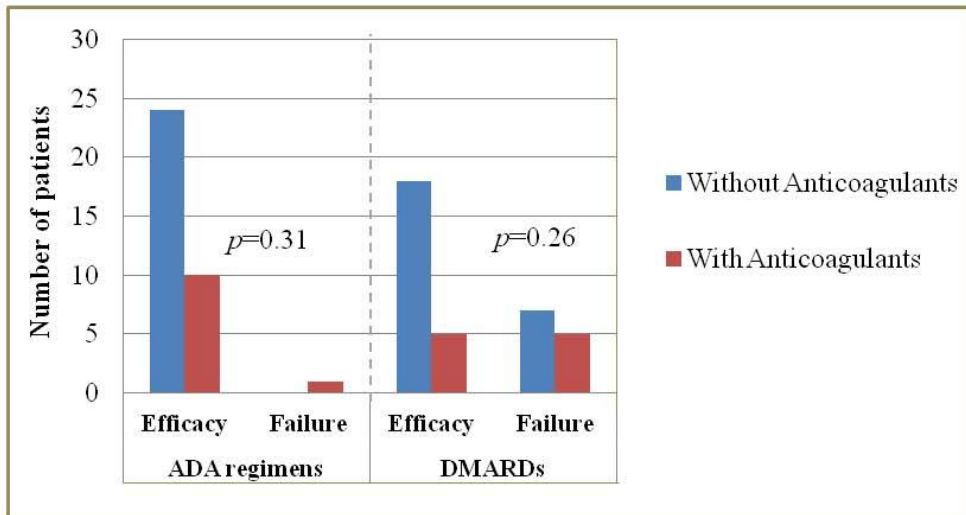
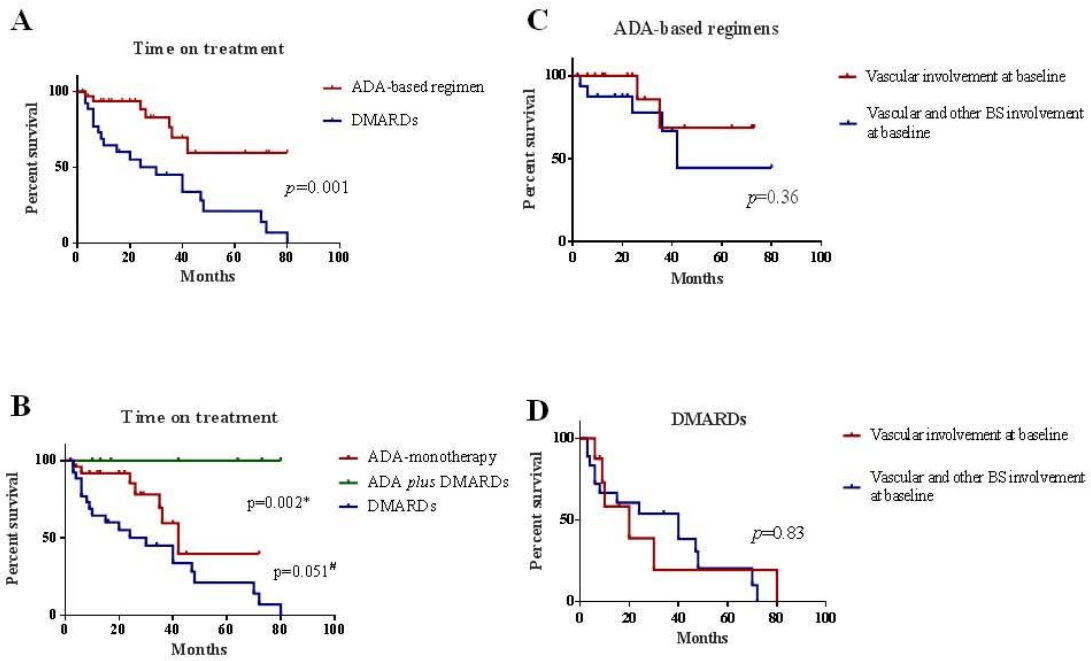
**Table 1** Demographic and clinical features of patients enrolled in the study and clinical manifestations recorded at the start of ADA-based regimen or DMARDs therapy.

	<b>ADALIMUMAB-BASED REGIMEN</b>	<b>DMARDs ALONE</b>	<b>p-value</b>
Gender, M/F	18/17	19/16	0.81
Age, years	42.8±11.2	53.8±32.1	0.009
Disease duration, months	106.6±107.5	123.4±113.9	0.29
ICBD fulfillment	35 (100)	35 (100)	> 0.99
HLA-B51 positivity	22 (62.9)	23 (65.7)	> 0.99
Oral aphthosis	35 (100)	35 (100)	> 0.99
Genital aphthosis	14 (40)	15 (42.9)	> 0.99
Ocular involvement	17 (48.6)	15 (42.9)	0.81
Skin manifestations	23 (65.7)	23 (65.7)	> 0.99
Arthritis/arthritis	17 (48.6)	18 (51.4)	> 0.99
Intestinal involvement	11 (31.4)	14 (40)	0.62
Neurologic manifestations	7 (20)	11 (31.4)	0.41
Vascular involvement	35 (100)	35 (100)	> 0.99
<b>Other than vascular BS manifestations at the start of treatments</b>			
Oral aphthosis	22 (62.9)	20 (57.1)	0.80
Genital aphthosis	8 (22.9)	6 (17.1)	0.77
Ocular involvement	6 (17.1)	9 (25.7)	0.56
Skin manifestations	3 (8.6)	2 (5.7)	> 0.99
Arthritis/arthritis	2 (5.7)	0 (0)	0.49
Intestinal involvement	1 (2.9)	2 (5.7)	> 0.99
Neurologic manifestations	2 (5.7)	4 (11.4)	0.67
<b>Specific vascular manifestations</b>			
Unilateral SVT	6 (17.1)	11 (31.4)	0.16
Bilateral SVT	9 (25.7)	4 (11.4)	0.22
Unilateral DVT	17 (48.6)	17 (48.6)	>0.99
Bilateral DVT	11 (31.4)	7 (20)	0.41

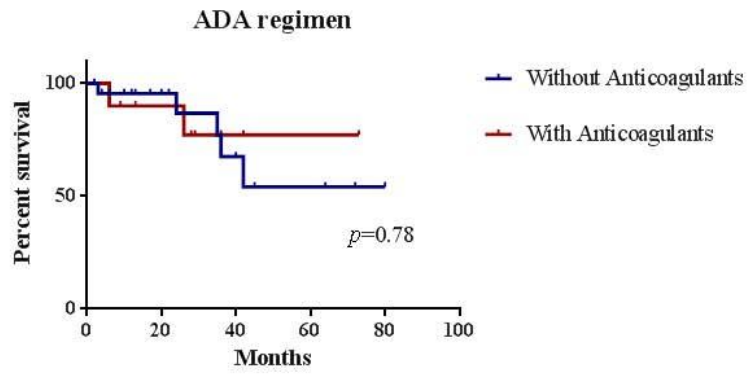
Data are shown as n(%) or as mean ± standard deviation. P-values were calculated with Fisher Exact Test for qualitative variables and Mann-Whitney U test for quantitative data after having assessed the non parametric distribution with Anderson-Darling test.

**List of abbreviations:** ADA, adalimumab; BS, Behçet syndrome; DMARDs, disease modifying anti-rheumatic drugs; DVT, deep vein thrombosis; ICBD, International Criteria for Behçet Disease; HLA, human leukocyte antigen; SVT, superficial vein thrombosis.





A



B

