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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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Objective. **Since Behçet's syndrome (BS) is the prototype of inflammation-induced thrombosis, immunosuppressants are recommended in place of anticoagulants. We undertook this study to assess the clinical efficacy and the corticosteroid-sparing effect of adalimumab (ADA)–based treatment versus disease-modifying antirheumatic drug (DMARD) therapy in a large retrospective cohort of patients with BS-related venous thrombosis.**

Methods. **We retrospectively collected data on 70 BS patients treated with DMARDs or ADA-based regimens (ADA with or without 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 ± SD follow-up period of 25.7 ± 23.2 months, ADA-based regimens induced clinical and imaging improvement of venous thrombosis more frequently ($P = 0.001$) and rapidly ($P < 0.0001$) than did DMARDs. The mean dose of corticosteroids administered at the last follow-up visit was significantly lower with ADA-based regimens than with DMARDs ($P < 0.0001$). The time on treatment was significantly longer with ADA plus DMARDs than with DMARDs alone ($P = 0.002$). No differences were found in terms of efficacy and time on treatment between DMARDs or ADA-based regimens among patients who received anticoagulants and those who did not.**

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

Behçet's syndrome (BS) is a systemic vasculitis characterized by protean manifestations such as mucocutaneous and ocular lesions as well as articular, neurologic, gastrointestinal, and vascular involvement (1). 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

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patients (2). 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 (3). 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 (4,5).

Recently, several studies have shown the efficacy of anti–tumor necrosis factor (anti-TNF) agents for BS-related vascular complications (6–9), especially for patients with arterial involvement (10). However, there are no prospective controlled trials or large retrospective studies focusing 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 on patients diagnosed as having BS and treated with DMARDs as the sole immunosuppressive therapy or with ADA-based regimens (ADA alone or combined with DMARDs) because of recurrent venous vascular manifestations. All patients were seen at the Behçet

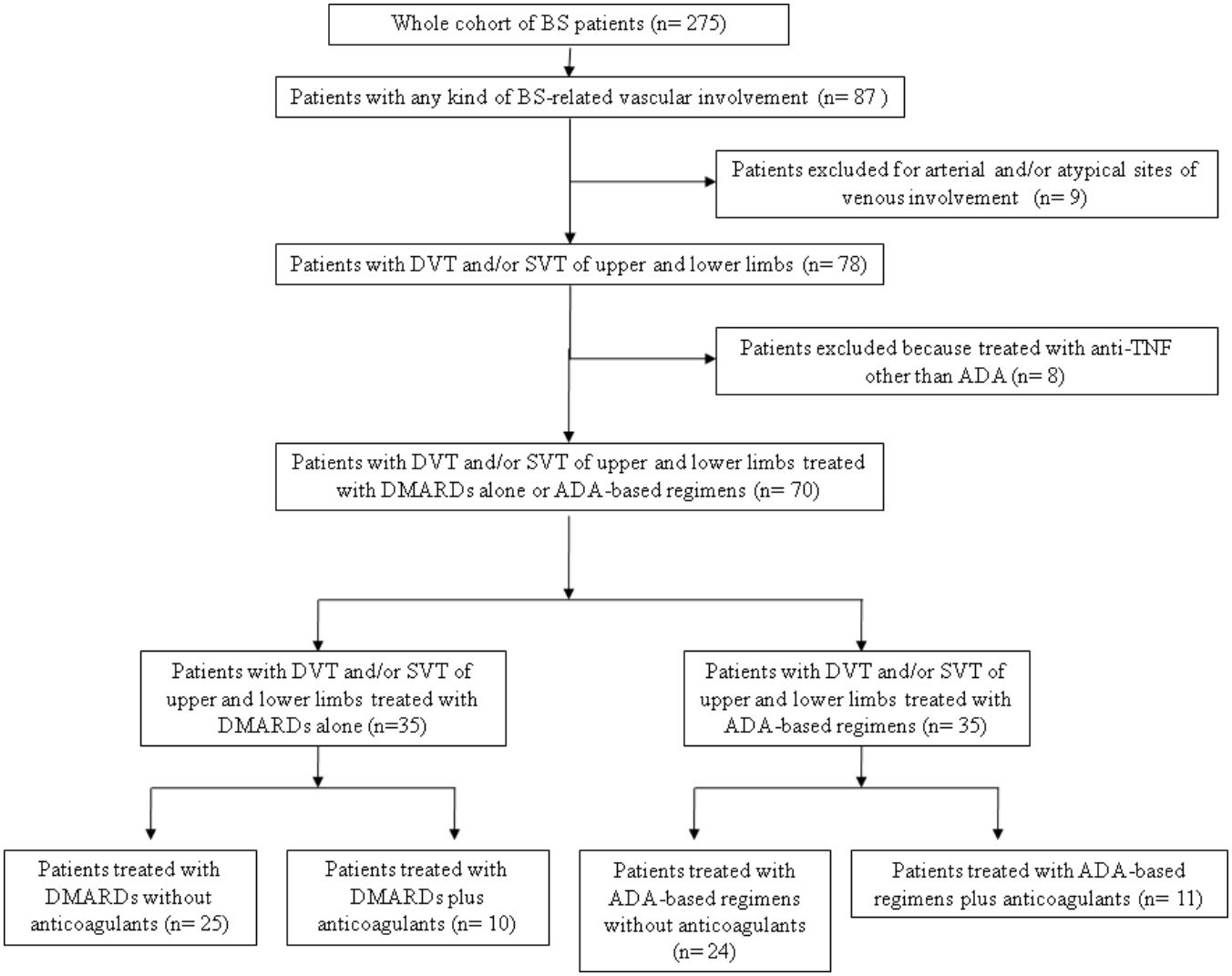

Figure 1. Study flow diagram. BS = Behçet's syndrome; DVT = deep vein thrombosis; SVT = superficial vein thrombophlebitis; anti-TNF = anti–tumor necrosis factor; ADA = adalimumab; DMARDs = disease-modifying antirheumatic drugs.

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 (11). 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).

In accordance with our clinical practice, patients with venous events were clinically and sonographically evaluated every 4 weeks for the first 3 months after the event, and then every 3 months or in case of BS relapse; all ultrasounds were performed by the same trained vascular ultrasound specialist (MB). DVT and SVT were diagnosed by the appearance of bilateral compression of upper or lower limb on ultrasound. Diagnostic criteria were cross-sectional vein incompressibility, direct thrombus imaging with vein enlargement, and abnormal spectral and color Doppler flow (12). The Doppler ultrasound response was defined as follows: 1) complete resolution of venous thrombosis; 2) partial response with revascularization, characterized by the presence of non–hemodynamically relevant parietal thrombosis; 3) 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 both a clinical and imaging 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 imaging response. Globally, both complete response and partial response have been defined in the text as "vascular response." The occurrence of postthrombotic syndrome was not considered in the evaluation of vascular outcome.

The data collected included age at BS onset, HLA–B51 positivity, clinical manifestations occurring 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 visit 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 1) to explore differences in the efficacy of treating SVT and DVT between ADA-based regimens and DMARDs alone, focusing on response rates and time to vascular response; 2) to compare the corticosteroid-sparing role of ADA-based regimens with that of DMARDs alone; 3) to compare the time on treatment with ADA-based regimens and DMARDs alone; and 4) to evaluate the role of concomitant anticoagulant therapy on vascular responses in patients treated with ADA-based regimens or DMARDs alone.

GraphPad Prism 6.0 software was used for statistical computation. Continuous variables are reported as the mean ± SD or the median (range) as appropriate, and categorical variables are reported as the number (%). For pairwise comparisons, the Mann-Whitney U test was used for continuous variables after having determined their non-Gaussian distribution using the Anderson–Darling test; Fisher's exact test was used for categorical variables. We analyzed 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 visit, by using the Kaplan-Meier method. Statistical differences in survival rates were assessed using the Mantel-Cox log rank test. *P* values less than 0.05 were considered 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 center during the study period, 78 had had DVT and/or SVT of the upper or lower limbs. Eight of the 78 patients were excluded from this study because they had been treated with anti-TNF agents other than ADA. The remaining 70 patients (37 men and 33 women) were included in the

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

	ADA-based regimens	DMARDs alone
Demographic and clinical features		
No. of men/women	18/17	19/16
Age, mean ± SD years	42.8 ± 11.2	53.8 ± 32.1
Disease duration, mean ± SD months	106.6 ± 107.5	123.4 ± 113.9
Meeting ICBD	35 (100)	35 (100)
HLA–B51 positive	22 (62.9)	23 (65.7)
Oral aphthosis	35 (100)	35 (100)
Genital aphthosis	14 (40)	15 (42.9)
Ocular involvement	17 (48.6)	15 (42.9)
Skin manifestations	23 (65.7)	23 (65.7)
Arthritis/arthralgia	17 (48.6)	18 (51.4)
Intestinal involvement	11 (31.4)	14 (40)
Neurologic manifestations	7 (20)	11 (31.4)
Vascular involvement	35 (100)	35 (100)
Other than vascular BS manifestations at the start of treatment		
Oral aphthosis	22 (62.9)	20 (57.1)
Genital aphthosis	8 (22.9)	6 (17.1)
Ocular involvement	6 (17.1)	9 (25.7)
Skin manifestations	3 (8.6)	2 (5.7)
Arthritis/arthralgia	2 (5.7)	0 (0)
Intestinal involvement	1 (2.9)	2 (5.7)
Neurologic manifestations	2 (5.7)	4 (11.4)
Specific vascular manifestations		
Unilateral SVT	6 (17.1)	11 (31.4)
Bilateral SVT	9 (25.7)	4 (11.4)
Unilateral DVT	17 (48.6)	17 (48.6)
Bilateral DVT	11 (31.4)	7 (20)

* There were no significant differences between the groups, with the exception of age ($P = 0.009$). Except where indicated otherwise, values are the number (%). ADA = adalimumab; DMARD = disease-modifying antirheumatic drug; ICBD = International Criteria for Behçet's disease; BS = Behçet's syndrome; SVT = superficial vein thrombophlebitis; DVT = deep vein thrombosis.

study (Figure 1). Among the enrolled patients, 35 (18 men and 17 women) had been treated with ADA-based regimens (ADA alone or combined with DMARDs) and 35 (19 men and 16 women) with DMARDs alone. Table 1 summarizes the demographic and clinical features of the 70 patients enrolled. Of the 35 patients who received DMARDs alone, 18 (51%) were treated with azathioprine, 9 (26%) with cyclosporine, 5 (14%) with cyclophosphamide, and 3 (9%) with methotrexate. Of the 35 patients treated with ADA, 27 received ADA monotherapy and 8 received ADA plus DMARDs (azathioprine in 7 patients and methotrexate in 1 patient). Apart from severe oral aphthosis, 10 of 35 patients treated with DMARDs alone and 16 of 35 treated with ADA-based regimens had vascular involvement as the sole disease manifestation at the start of therapy.

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

Among those who initially presented with SVT, vascular responses were observed in 3 of 4 patients (75%) treated with ADA-based regimens and in 3 of 7 patients (42.86%) treated with DMARDs alone ($P = 0.545$). ADA-based regimens were used in patients with SVT who had other disease manifestations (2 with ocular involvement, 1 with severe oral aphthosis and erythema nodosum, and 1 with 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% versus 33.33%; $P = 0.029$).

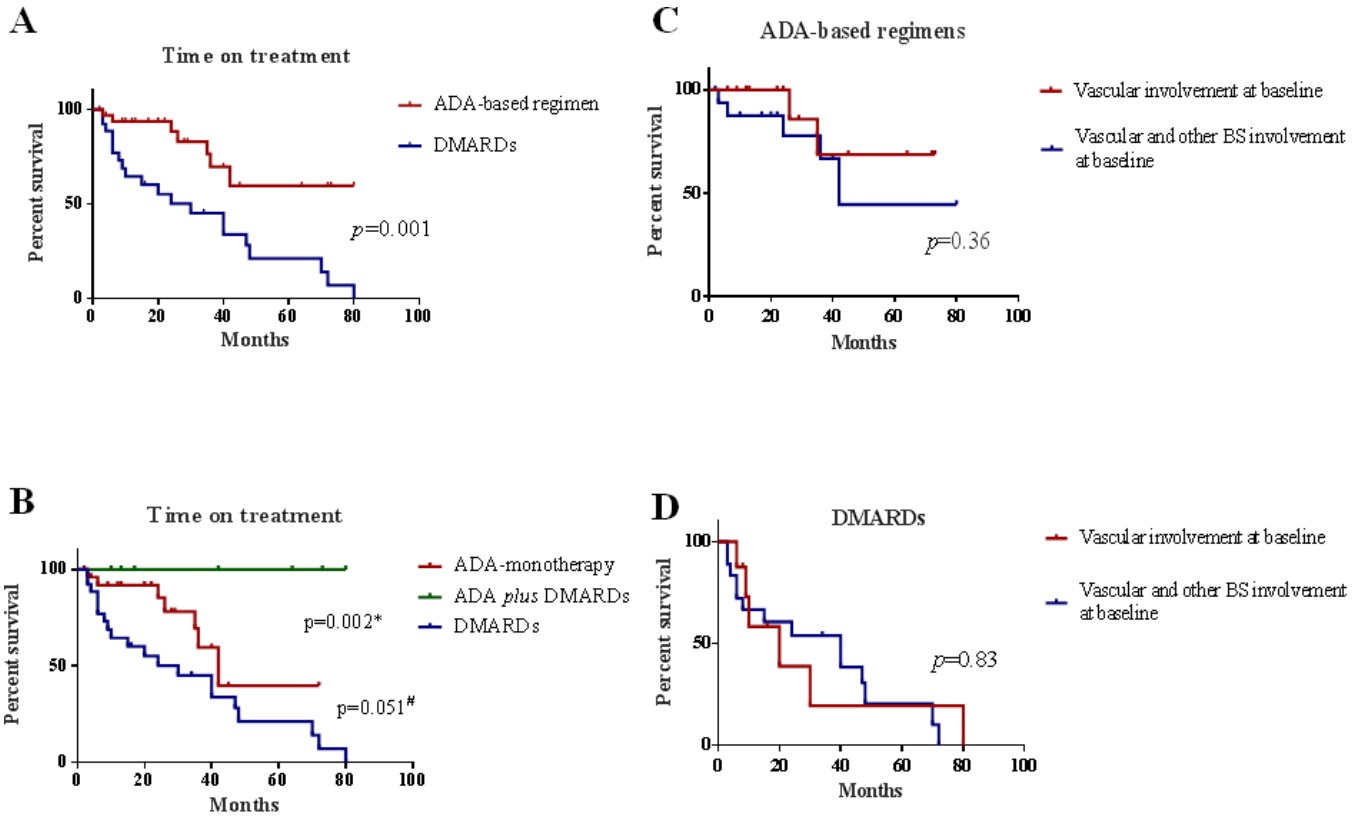

Figure 2. **A** and **B**, Overall time on treatment, assessed using the Kaplan-Meier method, in patients treated with adalimumab (ADA)–based regimens (alone or in combination with disease-modifying antirheumatic drugs [DMARDs]) and patients treated with DMARDs alone (**A**) and in patients treated with ADA monotherapy, patients treated with ADA plus DMARDs, and patients treated with DMARDs alone (**B**). In **B**, * = log rank *P* value for the comparison of ADA plus DMARDs with DMARDs alone; # = log rank *P* value for the comparison of ADA monotherapy with DMARDs alone. **C,** Survival rates with ADA-based regimens, in patients with Behçet's syndrome (BS)–related vascular involvement as the sole clinical manifestation at the start of treatment (baseline) and patients with additional BS manifestations at the start of treatment. **D,** Survival rates with DMARD treatment, in patients with BS-related vascular involvement as the sole clinical manifestation at the start of treatment (baseline) and patients with additional BS manifestations at the start of treatment.

The mean ± SD time required to achieve a vascular response (either complete or partial) was 3.7 ± 1.7 weeks for ADA-based regimens and 6.3 ± 1.2 weeks for DMARDs. The time to response was significantly shorter for those receiving ADA-based regimens than for those receiving DMARDs alone ($P < 0.0001$ by log rank test).

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

The mean ± SD prednisone dose administered at the last follow-up visit for isolated vascular involvement was 4.3 ± 3.8 mg/day in patients treated with ADA-based regimens and 10.2 ± 4.6 mg/day in patients treated with DMARDs alone ($P = 0.002$). The mean ± SD prednisone reductions for isolated vascular involvement were 20.0 ± 15.4 mg/day and 19.1 ± 17.2 mg/day in the ADA and DMARD groups, respectively ($P = 0.908$).

When we evaluated the time on treatment, we observed that it was significantly longer in all patients treated with ADA (both as monotherapy and combined with DMARDs) than in those treated with DMARDs alone ($P = 0.001$ by log rank test) (Figure 2A). Additionally, the time on treatment was significantly longer in patients who received ADA plus DMARDs than in those who received DMARDs alone ($P = 0.002$ by log rank test). 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 ($P = 0.051$ by log rank test) (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 (apart from oral aphthosis) at the start of therapy and those having other disease manifestations ($P = 0.36$ by log rank test) (Figure 2C). A comparable time on treatment was also observed in DMARD-treated patients with or without other disease manifestations ($P = 0.83$ by log rank test) (Figure 2D).

During the follow-up period, 9 of 35 patients (25.7%) discontinued ADA, due to lack of efficacy (1 patient), loss of efficacy for vascular and extravascular manifestations (3 patients each), and the occurrence of generalized urticarial skin rash after ADA injection (2 patients). With regard to the 3 subjects with vascular relapse who had originally responded to ADA, 1 with an initial stroke had a new stroke, 1 with initial bilateral SVT had a recurrence of bilateral SVT, and 1 with initial bilateral SVT and unilateral DVT experienced a new unilateral DVT. Among patients treated with DMARDs, 27 of 35 (77.1%) switched to other therapies, because of lack of efficacy (6 patients), loss of efficacy (17 patients [14 for vascular relapses]), adverse events (2 patients), and failure of compliance (2 patients). Among the 14 patients with vascular relapse after DMARD therapy, 5 with an initial DVT had a new DVT, 2 with an initial SVT re-experienced SVT, and 1 with an initial DVT developed an SVT; the remaining 6 patients, who presented with both SVT and DVT at diagnosis, had a new SVT (3 patients), a new DVT (1 patient), or both an SVT and a DVT (2 patients).

The proportion of patients who discontinued therapy because of loss of efficacy over time was significantly higher among patients treated with DMARDs ($P = 0.01$).

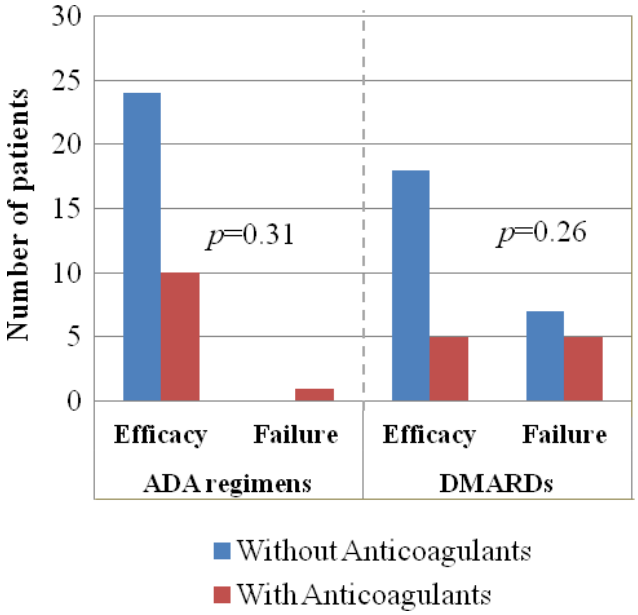

Figure 3. Frequency of responsiveness to adalimumab (ADA)–based regimens and disease-modifying antirheumatic drugs (DMARDs) alone, with patients grouped according to the concomitant use of anticoagulants. *P* values were obtained by Fisher's exact test and compare the frequency of efficacy (complete plus partial response) of ADA-based regimens and DMARDs between patients who were receiving anticoagulants and those who were not. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.40531/abstract.

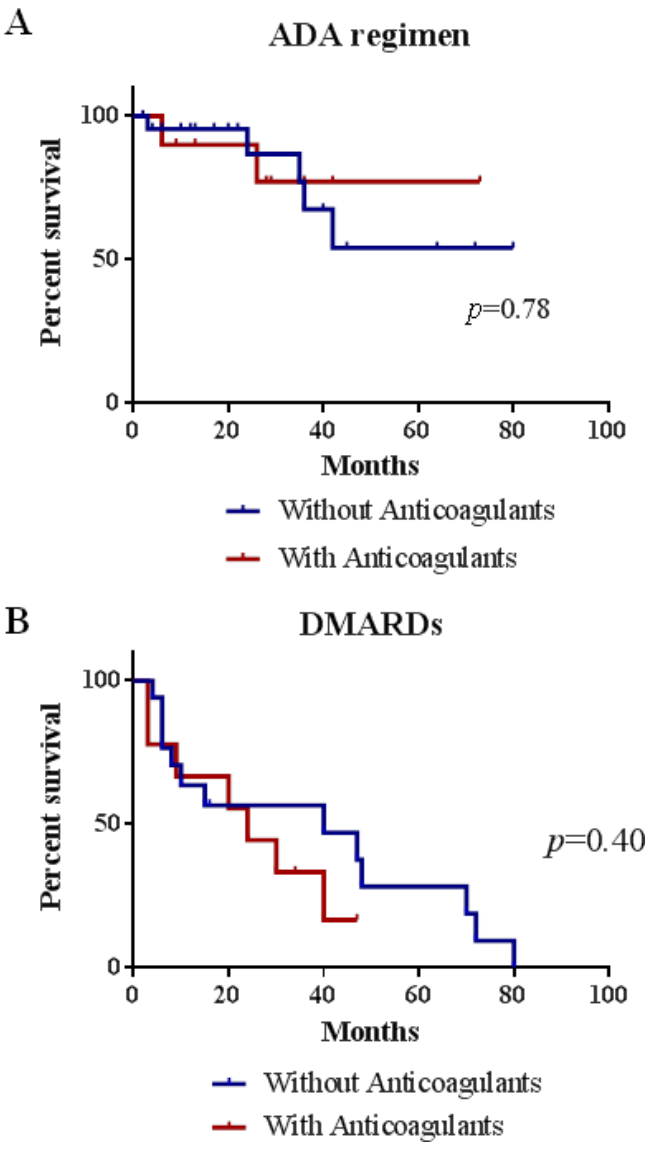

Figure 4. Survival rates with adalimumab (ADA)–based regimens (**A**) and regimens consisting of disease-modifying antirheumatic drugs (DMARDs) alone (**B**), with patients grouped according to the concomitant use of anticoagulants. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.40531/abstract.

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

We also assessed the effect of concomitant anticoagulant therapy on vascular responses. Concomitant warfarin therapy was given to 11 of 35 patients treated with ADA-based regimens (7 of whom had DVT and 4 of whom had both DVT and SVT) and to 10 of 35 patients treated with DMARDs (1 of whom had recurrent SVT, 1 of whom had DVT, and 8 of whom had 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 patients who were receiving anticoagulants and those who were not (Figure 3). In addition, the survival rates with ADA-based regimens or DMARDs alone did not differ significantly between patients who received anticoagulants and those who did not (P = 0.78 and P = 0.40, respectively) (Figure 4). In relation to the safety profile, 1 case of herpes zoster virus reactivation and 1 case of pneumonia were recorded among patients treated with ADA-based regimens, along with the 2 aforementioned cases of generalized skin rash.

DISCUSSION

Vascular involvement in BS represents a clinical issue in terms of morbidity and mortality (13), and optimal clinical management still remains a matter of debate (14,15). Anti-TNF agents are increasingly reported as the treatment of choice for involvement of different organs in BS (5,16–20); nevertheless, only few data are available on the role of TNF inhibition in BS patients with vascular involvement (10,21).

To the best of our knowledge, our study represents the largest experience with the use of TNF blockers for typical BS-related venous thrombosis. Indeed, although venous thromboses (both DVT and recurrent SVT) are the most frequent vascular manifestations in BS (13,22,23), the role of TNF inhibitors has been mainly reported in patients with arterial complications (10), especially those involving pulmonary vessels (24–26). In contrast, infliximab has been described as minimally effective in patients with atypical venous involvement (Budd-Chiari syndrome) (21), while its efficacy for DVT of the lower limbs has been only anecdotally reported (27).

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 to DMARDs. Consequently, as venous thrombosis requires early treatment that can induce a quick response, TNF inhibition may represent an optimal therapy in this clinical setting.

Anti-TNF agents have already been described as having a corticosteroid-sparing effect in BS patients (9,28), but specific data on patients 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 DMARDs at the start of treatments, steroid dosage was significantly lower among patients 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 glucocorticoid-induced side effects in BS patients.

In our study, the proportion of patients discontinuing treatment due to loss of efficacy over time was significantly higher among those receiving DMARDs than among those receiving ADA-based regimens. Moreover, patients receiving ADA-based regimens (both as monotherapy and combined with DMARDs) continued treatment for a longer period of time than those given DMARDs alone, with >50% of patients who received ADA-based regimens continuing treatment after 80 months. Intriguingly, the time on treatment was significantly longer for patients receiving combination therapy (ADA plus DMARDs) than for those receiving DMARDs alone. Similarly, patients receiving ADA monotherapy tended to do so for a longer period of time than patients receiving DMARDs alone. These data parallel those previously reported in other chronic inflammatory conditions, such as rheumatoid arthritis (29). Of note, no differences were found in 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 to clinicians, since apart from classic manifestations such as oral and genital aphthous/ulcerative lesions, the clinical phenotypes of BS are extremely diverse (30). 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 (31–33). On the other hand, as recently pointed out by Seyahi and Yazici (34), anticoagulation in BS patients might still be of some help in nonendemic areas, where it is more difficult for clinicians not familiar with BS to correctly attribute vascular manifestations to BS itself.

In this context, anticoagulation in our patients influenced neither the response rate nor the time on treatment for ADA-based regimens and DMARD therapy. Nevertheless, these results should be interpreted 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 the 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 (35).

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 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 us to exclude these kinds of vascular involvement, while follow-up needed for arterial involvement is different from that for venous involvement. However, some strengths of our study warrant mention as well. This is the largest study to investigate the efficacy of ADA-based regimens compared to that of DMARDs alone for venous thrombosis, and it is the only one to consider a homogeneous vascular involvement (DVT and/or SVT of lower and upper limbs). These data shed some light on one of the major complications of BS, indirectly confirming our previous experimental data on the inflammatory nature of venous thrombosis in this condition (3). Indeed, vascular involvement in BS represents a unique example of inflammation-induced thrombosis; experimental data (3), previous clinical experience (4), 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 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 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 minimization 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 plays a role in the pathogenesis of vascular complications in BS. Prospective controlled studies to corroborate our findings are warranted.

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. G. Emmi 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.

Study conception and design. G. Emmi, Vitale, Vaglio, Cantarini.
Acquisition of data. Silvestri, Boddi, Becatti, Fiorillo, Fabiani, Frediani, L. Emmi, Di Scala, Goldoni.
Analysis and interpretation of data. G. Emmi, Vitale, Bettiol, Vaglio, Cantarini, Prisco.

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