Adherence to guidelines for the treatment of Behçet's syndrome in New York and Amsterdam

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Received on October 8, 2016; accepted in revised form on February 23, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 108): S55-S59.

Key words: Behçet's syndrome, guideline adherence, treatment

Competing interests: Y. Yazici has received research support from BMS; the other authors have declared no competing interests.

ABSTRACT

Objective. *To assess adherence to published guidelines for the treatment of Behçet's syndrome (BS) in two geographic areas.*

Methods. *We extracted guideline statements from the 2008 EULAR recommendations. Adherence to these statements was evaluated retrospectively in both New York (USA) and Amsterdam (The Netherlands), by reviewing records from patients fulfilling the ISG criteria. We analysed data per statement and event, and divided data according to the year in which an event occurred. We compared events prior to 2009 to those after publication of the EULAR recommendations (2009 and later).*

Results. *474 patients were evaluated, 24 of whom were from Amsterdam. Treatment adherence varied substantially across various Behçet's manifestations, ranging from 21% vs. 31% in posterior uveitis, 50% vs. 25% in arterial disease, 29% vs. 29% in arthritis and 38% vs. 55% in erythema nodosum to 65% vs. 67% in deep venous thrombosis (DVT), before and after publication of the guidelines respectively. Topical treatment of mucocutaneous disease was only 2% vs. 8%, whereas adherence in neuro-Behçet was ≥94% and 100% in gastrointestinal disease.*

Conclusion. *Adherence to treatment guidelines varies substantially by Behçet manifestation. Lack of adherence in manifestations such as eye disease and arthritis suggests that current recommendations are not sufficient or other concurrent manifestations require more aggressive treatment. The extensive use of anti-TNF agents might indicate a shift towards more aggressive treatment. Thus, our results suggest the 2008 guidelines were not in line with treatment in clinical practice over the past years and the recent revision of the recommendations was indeed needed.*

Introduction

Behçet's syndrome (BS) is a systemic vasculitis most commonly seen in regions along the Silk Road. The exact aetiology of the disease remains unknown (1-4). Clinical manifestations of BS consist of recurrent oral ulcers (OU), genital ulcers (GU), ocular inflammation, skin disease, arthritis and gastrointestinal and central nervous system (CNS) involvement and may vary with ethnic origin (5-7). The disease has a relapsing/remitting course and it tends to be more severe in young males with diminishing activity in both males and females with age (8).

Because of the relapsing/remitting course of the disease and the variety of symptoms and organs involved, treatment of BS depends on severity of the manifestations (9-11). Lack of controlled data on treatment of certain manifestations of the disease (i.e. CNS involvement) leads to a wide variety in treatment approaches. In general, there seems to be a tendency for more intensive treatment of BS over the past decades (12-14).

A EULAR task force was assembled to provide clarity on current evidence and develop evidence-based recommendations for treatment of BS (15). Since 2008, when these guidelines were published, new treatment options based on insight in treatment of rheumatic diseases, BS included, were developed and recently, a revision of these guidelines has been announced at EULAR 2016 by Hatemi *et al.* (15-18).

In this study, we evaluated adherence to the 2008 EULAR recommendations. In order to assess whether treatment has changed due to implementation of the recommendations, we compared treatment before and after publication of these guidelines.

Methods

In this observational study, we included consecutive patients, fulfilling the 1990

Table I. Statements extracted from 2008 EULAR recommendations.

	Statement
1	Inflammatory eye disease affecting the posterior segment should be treated with a regime that includes azathioprine and systemic corticosteroids.
2	Severe eye disease, defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease should be treated with a) AZA and corticosteroids in combination with cyclosporine A or infliximab OR b) IFN-α (with or without corticosteroids).
3	Acute deep vein thrombosis should be treated with immunosuppressive medication such as corticosteroids, azathioprine, cyclophosphamide or cyclosporine A.
4	Pulmonary and peripheral arterial aneurysms should be treated with cyclophosphamide and high dose corticosteroids.
5	In case of DVT or arterial thrombosis, the following pharmacological agents are not recommended: anticoagulants, antifibrinolytic or antiplatelet agents.
6	In case of gastrointestinal involvement, pharmacological agents should be used prior to surgical treatment, except in emergencies.
7	Arthritis should be treated with colchicine.
8	Parenchymal CNS involvement should be treated with one of the following pharmacological agents: corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate and TNF-α antagonists.
9	Dural sinus thrombosis should be treated with corticosteroids.
10	Cyclosporine A should NOT be used in case of CNS involvement, unless required for ocular disease.
11	Oral and genital ulcers and acne vulgaris should be treated first line with topical agents (corticosteroids or treatment commonly used in acne vulgaris).
12	Erythema nodosum should be treated with colchicine.
13	If topical treatment is not sufficient in treating mucocutaneous manifestations, AZA, IFNα or anti-TNF should be used.

AZA: Azathioprine; CNS: central nervous system; DVT: deep venous thrombosis; IFN: interferon; TNF: tumour necrosis factor.

ISG criteria for BS from our outpatient clinics in New York (NYULMC) and Amsterdam (Reade) (19); patients with a probable Behçet's diagnosis were not included. Research was in compliance with the Helsinki Declaration, and the protocol was approved by the institutional review board (IRB) at each participating site. Physicians (YY and FT) recorded current and past clinical manifestations as well as treatment given for all Behçet patients, at both first (both centres) and follow up visits (NY patients only).

Based upon the 2008 EULAR guidelines (20), a Behçet's treatment checklist was created to assess guideline adherence. If guidelines were not followed, the actual treatment dispensed was recorded. Partial adherence was defined as a patient being treated with some, but not all, of the recommended medications. If none of the recommended medications were used, this was considered nonadherence.

Corresponding manifestation and treatment data were divided according to the year in which an event occurred: events prior to 2009 or events occurring in 2009 or later (after publication of the EULAR recommendations). The association of improved treatment adherence occurring post-publication of the EULAR guidelines was estimated using Chi-Square test of independence; Fisher's Exact test was used if assumptions for Chi-Square could not be maintained. Each individual assessment and corresponding treatment decision of a manifestation was considered to be independent. Statistical analysis was completed using Stata 14.1 (College Station, TX). Lastly, we recorded the number and type of concurrent disease manifestations.

Results

474 patients were evaluated, 24 of whom were from Amsterdam. Mean age was 37.9 years and 77% were female. Data on ethnicity were missing in 45 patients, 320 patients were Caucasian, 24 patients were Asian, 19 African-American, 34 Hispanic and 32 patients were Mediterranean.

Adherence varies substantially between the different types of manifestations analysed (Table II).

Guideline adherence in severe ocular disease and arterial disease could not be evaluated properly. The number of events was too small for any comparison of time frames and significant conclusion. Also, topical treatment of mucocutaneous manifestations was not systematically recorded in our database and therefore, could not be evaluated.

Uveitis

In posterior uveitis, the guideline was followed in 3 out of 14 (21%, 95% confidence interval (CI) 0–42%) patients prior to 2009 and 19 out of 62 (31%, 95%-CI 20-42%) after 2009. Partial adherence was 36% (5/14 patients, 95% CI 11–61%) and 48% (30/62 patients, 95%-CI 32–64%) for the given time frames, respectively. In the first time frame all patients with partial adherence were on azathioprine. In the second time frame 12 patients (40%) were on corticosteroids and 18 patients (60%) were on azathioprine. However, further analysis of data showed that prior to publication of the guidelines, 20% of patients with partial adherence (either corticosteroids or AZA) and 83% of patients with nonadherence (neither corticosteroids nor AZA) were on treatment with a biologic DMARD (infliximab, adalimumab or etanercept) or cyclosporine. After publication of the guidelines, 66% of cases with partial adherence and 77% with nonadherence were on a biologic DMARD or cyclosporine.

Data showed non-adherence in 36% (95%-CI 15–57%) and 21% (95%-CI 11–31%) of patients with uveitis before and after publication of the guidelines, respectively. In the first time frame, 1 patient was treated with steroid eye drops only, 2 patients were on azathioprine monotherapy, 1 patient was on azathioprine and colchicine and 1 patient was on steroid eye drops, colchicine and azathioprine. As for the second time frame, 1 patient was on no

Table II. Guideline adherence in treatment of 474 patients with Behçet's syndrome.

Event (n events in n of patients) *EULAR recommendation*	Adherence	% Before 2009 (n events)	% 2009-present (n events)
Posterior uveitis (76 in 59 pts)	Yes	21% (3)	31% (19)
Systemic corticosteroids + AZA	Partial	36% (5)	48% (30)
	No	43% (6)	21% (13)
Severe ocular disease/retinal involvement (11 in 11 pts)	Yes	25% (1)	57% (4)
Add Cyclosporine or IFX; or treat with IFN	Partial	50% (2)	29% (2)
	No	25% (1)	14% (1)
Vascular arterial disease (10 in 10 pts)	Yes	50% (3)	25% (1)
Cyclophosphamide and high dose corticosteroids	Partial	50% (3)	25% (1)
	No	0% (0)	50% (2)
Vascular – DVT (29 in 29 pts)	Yes	65% (13)	67% (6)
Corticosteroids, AZA, cyclophosphamide or cyclosporine	No	35% (7)	33% (3)
Anticoagulants, antifibrinolytic or antiplatelet agents (58 in 58 pts)	Yes	70% (23)	64% (16)
Not recommended	No	30% (10)	36% (9)
Gastrointestinal involvement (134 in 94 pts)	Yes	100% (34)	100% (100)
Drugs (immune suppressants) before surgery, except in case of emergency			
Arthritis (347 in 192 pts)	Yes	29% (24)*	29% (76)*
Colchicine	No	71% (58)	71% (189)
Neurological disease (47 in 35 pts)	Yes	100% (18)**	100% (28)
No cyclosporine, unless ocular inflammation			
Neurological disease – parenchymal disease (46 in 40 pts)	Yes	94% (17)	100% (28)
Corticosteroids, IFN-α, AZA, cyclophosphamide, methotrexate or TNF-α antagonists	No	6% (1)	
Erythema nodosum (114 in 88 pts)	Yes	38% (10)	55% (47)
Colchicine	No	62% (16)	45% (41)

Pts: patients; AZA: azathioprine; IFX: infliximab; IFN: interferon; DVT: deep venous thrombosis.
*Adherence if use of interferon α, azathioprine and anti-TNF agents is also taken into account is as high as 70% *vs*. 69%.
**1 patient with eye disease was on cyclosporine.

Table III. Concurrent symptoms in 192 BS patients with arthritis.

Symptom	Before 2009 n of events (in n pts)	2009 - present n of events (in n pts)
Oral ulcers	46 (33)	207 (106)
Genital ulcers	19 (13)	117 (82)
Pseudofolliculitis / papulopustular lesions	10 (10)	49 (35)
Acneiform lesions	17 (15)	70 (41)
Posterior uveitis/retinitis	3 (3)	16 (13)
CNS	5 (5)	22 (19)
Erythema nodosum	6 (4)	15 (14)
Gastrointestinal disease	12 (10)	31 (27)
Thrombophlebitis	-	2 (2)
Vascular – arterial	-	1 (1)
Vascular – venous	-	-
DVT	-	2 (2)
No concurrent symptoms	17 (13)	35 (25)
Total number of concurrent events	145	532

CNS: central nervous system; DVT: deep venous thrombosis.

treatment at all, 1 patient was on steroid eye drops, 1 patient was treated with colchicine, 8 patients were on azathioprine monotherapy and 2 on prednisone monotherapy. The actual treatment dispensed could not be retrieved completely in each patient or event.

Deep vein thrombosis

Regarding the treatment of deep venous thrombosis (DVT) with immune suppressants as well as anticoagulants, no significant change was observed when comparing the two time frames. Sixty-five percent of patients with deep venous thrombosis were treated in accordance to guidelines prior to 2009 (95%-CI 45–85%), compared to 67% after 2009 (95%-CI 10–100%). Of all patients with vascular disease, 70% (95%-CI 54–86%) was not on anticoagulants before publication of the guidelines and 64% (95%-CI 45–83%) after publication.

Gastrointestinal involvement

Guideline adherence in gastrointestinal disease was 100%, *i.e*. primarily pharmacological therapy was given rather then surgical intervention (Table I, statement 6). One emergency surgery was performed before the patient was started on any medication. Furthermore, one patient needed surgery, albeit on immune suppressants.

Arthritis

Colchicine in treatment of arthritis was used as monotherapy in 3 cases (4%, 95%-CI 0–8%) before 2009 *vs*. 9 cases (3%, 95%-CI 1–5%) after 2009. Additional drugs used included prednisone (n=197), hydroxychloroquine (n=63), methotrexate (n=67), azathioprine (n=133) and anti-TNF agents (n=124). According to the guidelines, interferon α, azathioprine and anti-TNF agents can be used if colchicine is not sufficient. This would increase adherence, with 70% of cases before publication of the guidelines receiving one of these drugs (95%-CI 60–79%). After 2009, adherence including colchicine, azathioprine and anti-TNF agents was 69% (95%-CI 63–75%). Interferon α was not used in the treatment of arthritis in any of the records reviewed.

In 17 (21%) cases of arthritis prior to 2009, no concurrent symptoms were present. In 16 individual patients (with posterior uveitis/severe eye disease, neurological symptoms or gastrointestinal disease), concurrent symptoms required more intensive treatment.

In all but three cases of arthritis after 2009 (99%), concurrent symptoms were present. 61 individual patients

Table IV. Concurrent symptoms in 88 BS patients with erythema nodosum.

Symptom	Before 2009 n of events (in n pts)	2009 - present n of events (in n pts)
Oral ulcers	10 (8)	53 (45)
Genital ulcers	8 (8)	36 (32)
Pseudofolliculitis / papulopustular lesions	3 (3)	12 (10)
Acneiform lesions	4 (4)	8 (6)
Posterior uveitis/retinitis	1 (1)	7 (7)
CNS	-	4 (4)
Arthritis	6 (4)	15 (14)
Gastrointestinal disease	1 (1)	6 (6)
Thrombophlebitis	2 (2)	-
Vascular – arterial	-	-
Vascular – venous	-	-
DVT	-	1 (1)
No concurrent symptoms	6 (4)	29 (17)
Total number of concurrent symptoms	35	142

CNS: central nervous system; DVT: deep venous thrombosis.

had posterior uveitis, severe eye disease, neurological or gastrointestinal symptoms, DVT or arterial disease (Table III).

Neurological involvement

Guideline adherence in neurological disease was good (94% pre *vs*. 100% post guideline publication), irrespective of the time frame. One patient was on cyclosporine, required by concurrent ocular disease.

Erythema nodosum

Before and after publication of the guidelines, adherence in erythema nodosum (EN) was 38% (95%-CI 19-57%) and 55% (95%-CI 45-65%), respectively.

Colchicine was used as monotherapy in a minority of cases (19% (5 cases) <2009, 9% (8 cases) >2009). Other drugs used were dapsone (n=2), corticosteroids (n=61), hydroxychloroquine (n=11), azathioprine (n=41), methotrexate (n=13), mycophenolate mofetil (n=3) and infliximab (n=8), adalimumab (n=5) and cyclophosphamide (n=1).

Concurrent symptoms were present in 81% of cases of EN prior to 2009, and in 100% in the second time frame, requiring intensive treatment in 2 and 16 individual patients, respectively (Table IV).

Discussion

In our study, adherence to the guidelines varies substantially across type of events: it is high in neuro-Behçet and gastrointestinal disease, but rather low in arthritis, ocular and mucocutaneous disease. Analysis of the data did not show any statistically significant difference in adherence between time frames. Recommendations on gastrointestinal disease and CNS manifestations are clear on the need for immune suppression. Our findings underline the widespread use of immunesuppressants, even before publication of the guidelines. Moreover, sufficient scientific work is lacking 8 years post guideline publication, with the most recent consensus statements being based mostly on case reports and expert opinion (21). We would recommend more studies and possibly global data registration in BS, in order to fill the gap.

In patients with uveitis, arthritis and erythema nodosum, adherence seems relatively low at first. This might partly be due to the strict interpretation of the statements we extracted from the EULAR 2008 recommendations (Table I). It is important to take into account the remarks the authors of the recommendations discussed. Furthermore, the majority of patients with BS who had arthritis or erythema nodosum also suffered concurrent symptoms, often requiring more intensive treatment. For example, when strictly considering colchicine use for arthritis as compliant with the recommendations, adherence seems low (29%). However, if use of interferon α, azathioprine and anti-TNF agents is also taken into account, this increases adherence to 70% before and 69% after publication of the guidelines.

Also, opinions on acceptable duration of symptomatic disease may have changed over time. For example in current western society, it is unusual to start steroid eye drops monotherapy in posterior uveitis, whereas 20 years ago colchicine was considered adequate treatment in patients with pending vena cava thrombosis (14, 22). Furthermore, as in other rheumatic diseases, patients with BS are tending to be treated much more aggressively when compared to the early nineties of the last century (14). The widespread use of TNF inhibitors as monotherapy for uveitis may have also contributed to the lack of adherence to the letter of the recommendations.

These findings suggest that the revision of the current guidelines presented in 2016 was due, given widespread use of other immunosuppressive medications and newly available studies of these medications.

The foremost limitation of our study is its retrospective nature. Although data were collected prospectively, and patients included consecutively, the questionnaires used in clinical practice were not specifically designed to evaluate our statements. This meant that information regarding some of the statements was not available in the database and could not be retrieved by reviewing records either. For example in uveitis, this may explain the undertreatment reported in our study. However, this design allowed us to review data from a large number of patients.

In conclusion, choices in the treatment of BS are quite concordant with some EULAR recommendations. When this was not the case, more intensive treatment seemed to be preferred. This may be due to either concurrent symptoms or evolving concepts of management of Behçet's syndrome.

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