Results of a questionnaire on the treatment of patients with Behçet's syndrome: a trend for more intensive treatment

F. Turkstra[1], R.M. van Vugt[2], B.A.C. Dijkmans[1,2], Y. Yazici[3], H. Yazici[4]

[1]Jan van Breemen Research Institute/ Reade, Amsterdam, the Netherlands; [2]VU Medical Centre, Amsterdam, the Netherlands; [3]NYU Hospital Joint Diseases, New York, USA; [4]Cerrahpasa University Istanbul, Turkey, for the TULIP working party.

Franktien Turkstra, MD, PhD
Richard M. van Vugt, MD, PhD
Ben A.C. Dijkmans, MD, PhD
Yusuf Yazici, MD
Hasan Yazici, MD

Please address correspondence and reprint requests to:
Franktien Turkstra,
Jan van Breemen Research Institute/ Reade,
P.O. Box 58271,
1040 HG Amsterdam, the Netherlands.
E-mail: f.turkstra@reade.nl

Received on May 20, 2011; accepted in revised form on December 13, 2011.

Clin Exp Rheumatol 2012; 30 (Suppl. 72): S10-S13.

Key words: Behçet's syndrome, treatment, questionnaire

Competing interests: none declared.

ABSTRACT

Objective. *To determine the preferred treatment for patients with Behçet's syndrome.*

Methods. *A questionnaire was given to all participants of the 2010 meeting of the International Society for Behçet's Disease.*

Results. *Forty-one respondents from 6 different subspecialties. In the case of a patient with (severe) posterior uveitis or parenchymal central nervous system (CNS) disease no consensus was seen. A diffuse spectrum of different schedules were given. In both uveitis and CNS disease the majority of respondents preferred treatment options consisting of combination systemic therapy and systemic corticosteroids. TNF was preferred as first line drug in uveitis in 7.5% and in severe uveitis in 32.5% of respondents. In parenchymal CNS disease TNF blockage was given by 17% of the respondents. EULAR guidelines regarding uveitis were followed by 12/40 physicians. In patients with a new deep vein thrombosis, 90% of respondents would intensify immunosuppression. More than half would also anticoagulate.*

Conclusion. *Although consensus about how to treat patients with Behçet syndrome in different clinical situations is far from present, treatment has become more intensive when compared to 10–20 years ago. More uniformity should be sought for in the decision process in individual patients with Behçet's syndrome, regarding their treatment, as well as adhering to evidence, as presented in the EULAR guidelines, when present.*

Introduction

Two physician questionnaires on the management of Behçet's syndrome (BS) have been published previously (1, 2), the last being more than ten years ago. During this time the EULAR guidelines on managing BS have also been available (3).

The purpose of the current survey was to re-assess the degree of consensus among physicians with special interest and expertise in BS about the preferred management of this entity. To this end we prepared a new questionnaire and distributed it to the participants of the London meeting of the ISBD (International Society for Behçet's Disease) in July 2010. The questionnaire was designed with clinical relevant situations which (partially) had been asked in the previous questionnaires as well.

Materials and methods

The ISBD 14th International Conference on Behçet's Disease, was held from 8–10 July 2010 in London. Several days before the conference all participants with a known e-mail address (approximately 270 people) received by e-mail a questionnaire (Table I). In the conference bag a paper copy of the questionnaire was also handed out to all participants and, finally, at the end of August 2010 a reminder was sent to all known e-mail addresses at that time (approximately 290 people). It is unknown how much overlap was present in the 2 mailings and the paper copy handout, thus a percentage of respondents could not be discerned.

Results

The total number of respondents was 41, with one questionnaire answered incompletely.

Fourteen answered the first e-mail, 8 the second, and 19 handed in the questionnaire at the conference.

Twenty-seven out of 40 responders practiced either in Europe or the USA, 7 resided in the Middle East and 6 respondents came from the Far East.

The majority, 31/40, respondents were either rheumatologists, immunologists or internists or a combination of these specialties. Four were dermatologists, 4 ophthalmologists and 1 was a paediatrician.

For the patient in the first question with posterior eye involvement, 17 different treatment options were preferred by 40 respondents, whereas 21 options were chosen in the patient with the severe eye disease (question 2). In the first patient all 4 ophthalmologists would have started systemic corticosteroids (100%, 95% CI 48%–100%), one combined it with corticosteroid eye drops and another with azathioprine. Systemic corticosteroids were part of the treatment strategy in the majority. Monotherapy corticosteroids was chosen by 9 respondents in the first patient, whereas the same was true for 2 respondents in the second patient. Azathioprine was given in 40%, and 32%, respectively in the setting of moderate (*i.e.* question 1) and severe (*i.e.* question 2) eye disease. Azathioprine was mostly given in combination therapy. Systemic combination therapy was given by the majority, 52 and 55% in moderate and severe uveitis, respectively. The EULAR guidelines for uveitis (3) which consist of the combination of systemic corticosteroids with azathioprine were followed in 30%, *i.e.* in 12 out of 40 respondents (95%CI 18%–46%). TNF blockade as first line treatment was answered in 7.5% and 32.5% in uveitis and severe uveitis respectively. Only two physicians selected corticosteroid eye drops as monotherapy, both for the first patient. In the patient with severe uveitis, two out of four ophthalmologists said that they would start monotherapy consisting of systemic corticosteroids, the third answered IFN monotherapy and the fourth answered he would start infliximab combined with cyclosporine.

When analysing whether there is a geographical influence in the difference in answers we compared respondents from the USA and European Union countries (27 respondents) with the rest of the world, including Japan and Turkey (13 respondents). There was no statistically significant difference in geographical preference in prescribing TNF blockers, nor in the number of physicians adhering to the EULAR guidelines. There was a significant geographical difference in prescribing systemic corticosteroids in patients with uveitis (in the EU and USA 22 out of 27 physicians (81%) answered they would do so, *versus* 6 out of 13 physicians residing in the rest of the world, *i.e.* 46%; p=0.0225). In severe uveitis no geographical difference was observed in starting systemic corticosteroids.

Regarding question 3 whether to treat a patient with grade one inflammation in the eye the majority of the respondents would start treatment (55%); and of the 4 ophthalmologists three would do so.

An old unsolved issue is whether or not to give anticoagulants or intensify immunosuppression or do both in patients with Behçet's syndrome and a new deep vein thrombosis. Ninety percent of the respondents would intensify immunosuppression (*i.e.* 36 out of 40 respondents), either alone (15 times) or in combination with anticoagulation (21 respondents). Four physicians answered they would start anticoagulation alone, without intensifying immunosuppression. Only 1 out of 27 physicians (4%) coming from the EU or USA would start anticoagulation alone.

For the case of a patient with parenchymal central nervous system disease 10 different types of preferred treatment were reported. Systemic corticosteroids were part of this treatment in 73% of respondents (30 out of 41). Cyclophosphamide was used by 18 respondents (44%) whereas TNF was preferred in

Table I. The questionnaire.

1. What is your preferred first line treatment in case the patient has eye disease with posterior segment inflammation? (Please tick ALL appropriate boxes in case of combination therapy).

☐ Corticosteroid eye drops ☐ Systemic corticosteroids ☐ Azathioprine
☐ IFN ☐ Cyclosporine ☐ Infliximab ☐ Adalimumab
☐ Etanercept
☐ different: please describe _____

2. What is your preferred treatment in case the eye disease is severe (Please tick ALL appropriate boxes in case of combination therapy):

☐ Corticosteroid eye drops ☐ Systemic corticosteroids ☐ Azathioprine
☐ IFN ☐ Cyclosporine ☐ Infliximab ☐ Adalimumab
☐ Etanercept
☐ different: please describe _____

3. A 40-year-old male with a 10-year history of Behçet's disease is found to have a few cells in the vitrea of both eyes on a routine follow-up visit. This is a new finding compared to one year ago. He is doing fine otherwise, apart from occasional mouth ulcerations. Would you agree not to prescribe any medications for his eyes at this time and just propose to follow him more closely?

☐ Yes ☐ No ☐ Not sure

4. What is your preferred treatment in a patient with Behçet's disease who has proven deep vein thrombosis?

☐ "intensify" immunosuppression ☐ anticoagulate with heparin (or LMWH) and/ or anticoagulant ☐ both?

5. What is your preferred first line treatment in case the patient has parenchymal CNS disease? (Please tick ALL appropriate boxes in case of combination therapy)

☐ Systemic corticosteroids ☐ Azathioprine ☐ Cyclophosphamide
☐ IFN ☐ Infliximab ☐ Adalimumab ☐ Etanercept
☐ different: please describe _____

6. Would you treat a 20-year-old male patient with a 6-month history of oral and genital ulceration along with erythema nodosum but no eye disease or other organ involvement, with Azathioprine for 2 years or more as a possible preventive measure against emergence of eye disease?

☐ yes ☐ no ☐ not sure

I am a ☐ rheumatologist ☐ internal medicine specialist ☐ immunologist
☐ ophthalmologist ☐ dermatologist ☐ neurologist ☐ other: please fill in _____
In case of trainee please tick: ☐
I am residing in: _____(country)

7, either alone or in combination with other systemic treatment modalities. No significant difference was observed when analysing the answers of physicians from the EU and USA compared to the rest of the world in both respects. Multiple systemic drug schemes were used in 20 out of 41 respondents.

Twenty-two out of 41 respondents would refrain from starting treatment in a young male patient with aphtae and erythema nodosum in order to prevent eye involvement. Almost one third would start treatment in this type of patient (*i.e.* 12/41), whereas the other 7 replied that they were not sure.

Discussion

There has been significant changes in the treatment of patients with rheumatic diseases in general, within the last decade. For example, in patients with rheumatoid arthritis it is clear that early intensive treatment is good for the short term, as well as long term (the so-called window of opportunity) (4). We saw a similar trend in BS in this survey.

Shortcoming to our survey were that the respondent rate was low at ~15%. There were no neurologists among the respondents. Finally, there were only 4 ophthalmologists.

Uveitis

In the 1991 questionnaire (1) a severe case of uveitis was treated with colchicine alone in 4/19 patients. The other physicians preferred treatment with either corticosteroids, cyclosporine A or azathioprine, or a combination of these (1). In a patient with moderately severe disease which was quiescent for two years, 4 out of 19 would give prophylactic treatment (21%).

In the 1999 questionnaire the majority of physicians agreed that steroids were useful in the treatment of retinal vasculitis (2). In mild eye disease, however, there was no consensus and 7 of 10 ophthalmologists deferred treatment and advised only watchful waiting (2).

Although consensus is still lacking (up to 21 different treatment schedules among 40 physicians) one thing has become clear: today the vast majority is advising more intensive treatment when compared to the 1990s. Especially the number of systemic multidrug treatment schemes is more than 50%. Also, the percentage of respondents agreeing to treat grade 1 inflammation is more than 50%, although direct evidence for this contention is still not at hand. Finally, although evidence from prospective trials is lacking 30% of respondents agree to start treating a high risk patient with only aphtae and erythema nodosum in order to prevent eye disease. This may be due to the promising "number needed to treat" in the Yazici 1990 study, where only two to three patients had to be given azathioprine in order to prevent an attack of eye inflammation (5). The EULAR guidelines committee concluded that further evidence for such prophylactic treatment still needs to be shown (3). A formal study investigating this is currently under way at Cerrahpasa Hospital, in Istanbul, Turkey.

It was sobering to note that only 8 of the 40 physicians (20%) in this survey were treating eye disease in accordance with the EULAR recommendations, which advise to treat every patient with inflammation of the posterior segment with azathioprine and systemic corticosteroids (3).

Deep vein thrombosis

In 1991 4/15 physicians would treat their patients with a pending vena cava superior obstruction with colchicine. In 1999 there was no consensus regarding the anticoagulant treatment of a patient with deep vein thrombosis. Now there is consensus: 90% of respondents gives more intensive immunosuppression, as is recommended in the EULAR guidelines (3). One issue remains to be solved since 52.5% will add anticoagulants as well. In a Korean retrospective study patients with anticoagulants alone had recurrent disease more often compared with those treated with additional immunosuppression (6). On the other hand case reports have been reported with Behçet's disease and other inherited prothrombotic states like protein C deficiency and factor V Leiden mutation who could not be managed without oral anticoagulant therapy (7). Clearly a work up for prothrombotic tendencies in a given patient should be done first before embarking on such treatment.

Neurologic involvement

In 1991 a quarter of the respondents would treat a patient with pyramido cerebellar involvement with colchicine, the other ¾ would give corticosteroids. In 1999 2/3 of the respondents agreed that corticosteroids are useful in the treatment of a patient with CNS disease. In 2008 the EULAR committee concluded that no controlled trials exist guiding treatment of patients with parenchymal CNS involvement (3).

In the current questionnaire a quite diffuse spectrum of treatment modalities is given. Patients are treated with multiple systemic drugs by 20/41of the physicians in the current survey.

Conclusions

In conclusion, current drug treatment in patients with Behçet's syndrome is more intensive. However, more uniformity in treatment should be sought for. As in the previous surveys, this lack of standardisation observed is most likely due to the relative paucity of evidence-based data coming from controlled drug trials. Specifically there is a definite need for controlled drug trials in neurological disease and thrombophilia, which should perhaps be conducted on a multinational basis.

Finally, even when there is rather satisfactory evidence coming from drug trials, as in uveitis, physicians can still follow their own preferences instead of the consensus-based guidelines. We strongly discourage this and propose a wider use of the EULAR guidelines which, while not perfect, are the best at hand.

References

1. YAZICI H, BARNES CG: A survey of treatment in Behçet's syndrome. *In*: O'DUFFY JD, KOKMEN E (Eds) *Behçet's disease. Basic and clinical aspects*. Marcel Dekker Inc., New York. 1991.
2. YAZICI H, YURDAKUL S, HAMURYUDAN V: The management of Behçet's syndrome: How are we doing? *Clin Exp Rheum* 1999; 17: 145-7.
3. HATEMI G, SILMAN A, BANG D *et al*.; EULAR EXPERT COMMITTEE: EULAR recommendations for the management of Behçet's disease. *Ann Rheum Dis* 2008; 67: 1656-62.
4. KLARENBEEK NB, GÜLER-YÜKSEL M, VAN DER KOOIJ SM *et al*.: The impact of four dynamic, goal-steered treatment strategies on the 5-year outcome of rheumatoid arthritis

patients in the BeSt study. *Ann Rheum Dis* 2011; 70: 1039-46. .
5. HATEMI G, SILMAN A, BANG D *et al*.: Management of Behçet disease: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for the management of Behçet disease. *Ann Rheum Dis* 2009; 68: 1528-34.
6. AHN JK, LEE YS, JEON CH, KOH EM, CHA HS: Treatment of venous thrombosis associated with Behçet's disease: immunosuppressive therapy alone versus immuno-suppressive therapy plus anticoagulation. *Clin Rheumatol* 2008; 27: 201-5.
7. KORKMAZ C, KASIFOGLU T, KEBAPCI M: Budd-Chiari syndrome in the course of Behçet's disease: clinical and laboratory analysis of 4 cases. *Joint Bone Spine* 2007; 74: 245-8.