EDITOR'S CHOICE

EULAR recommendations for the management of Behçet disease

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ABSTRACT

Objectives: To develop evidence-based European League Against Rheumatism (EULAR) recommendations for the management of Behçet disease (BD) supplemented where necessary by expert opinion.

Methods: The multidisciplinary expert committee, a task force of the EULAR Standing Committee for Clinical Affairs (ESCCA), consisted of nine rheumatologists (one who was also a clinical epidemiologist and one also a Rehabilitation Medicine doctor), three ophthalmologists, one internist, one dermatologist and one neurologist, representing six European countries plus Tunisia and Korea. A patient representative was also present. Problem areas and related keywords for systematic literature research were identified. Systematic literature research was performed using Medline and the Cochrane Library databases from 1966 through to December 2006. A total of 40 initial statements were generated based on the systematic literature research. These yielded the final recommendations developed from two blind Delphi rounds of voting.

Results: Nine recommendations were developed for the management of different aspects of BD. The strength of each recommendation was determined by the level of evidence and the experts' opinions. The level of agreement for each recommendation was determined using a visual analogue scale for the whole committee and for each individual aspect by the subgroups, who consider themselves experts in that field of BD. There was excellent concordance between the level of agreement of the whole group and the "experts in the field".

Conclusion: Recommendations related to the eye, skin–mucosa disease and arthritis are mainly evidence based, but recommendations on vascular disease, neurological and gastrointestinal involvement are based largely on expert opinion and uncontrolled evidence from open trials and observational studies. The need for further properly designed controlled clinical trials is apparent.

The aim of treatment in Behçet disease (BD) is to prevent irreversible damage that mostly occurs early in the course of disease, especially in the high-risk group, young men,[1 2] and to prevent exacerbations of mucocutaneous and joint involvement, usually not causing damage but affecting quality of life. The multisystem involvement mandates collaboration between different specialties.

Our aim was to develop recommendations for the management of BD, in line with the European Leage Against Rheumatism (EULAR)'s standardised operating procedures,[3] combining current evidence from clinical trials with expert opinion. The recommendations target all doctors and surgeons who are involved in the treatment of BD.

METHODS

The expert committee

The committee consisted of nine rheumatologists (one who was also a clinical epidemiologist and one also a rehabilitationist), three ophthalmologists, one internist, one dermatologist and one neurologist, representing six European countries plus Tunisia and Korea. A patient representative was also present.

Development of recommendations

The experts were invited to propose problem areas and related keywords regarding the management of BD before the first meeting; subsequently during the meeting 22 problem areas and 77 related keywords for systematic literature research were identified.

Medline (via PubMed) and The Cochrane Library were searched from 1966 to December 2006. The results of the systematic literature research were sent to the committee before the second meeting and proposals for recommendations were received. Before the second meeting, the convener (HY), the clinical epidemiologist (AS) and the bibliographic fellow (GH) went over the search results and the proposals, and tabulated 40 candidate statements to be further discussed by the committee. The Appraisal of Guidelines Research & Evaluation (AGREE) instrument was taken into consideration in preparing these statements.[4] During the second meeting these were discussed at length.

After the presentation of the literature research to the committee, each of the 40 statements was discussed and amendments were made and the number of statements was reduced to 25. A two-step Delphi exercise with closed voting followed. During the first round each of the 25 statements was separately voted on and given a score from 0 (absolutely no evidence or other information to support statement or recommendation) to 10 (available evidence provides maximal possible support). The committee agreed to omit the statements that received a mean score of less than 7.0. From the remaining statements, nine final recommendations were made after further discussion, editing and combining. The strength of each recommendation was determined using the traditional hierarchy (tables 1 and 2). Then, each final recommendation was again separately voted and scored. The voting was "blind" at all stages. The means and standard deviation of the scores of the whole group were calculated to determine the level

of agreement for each recommendation. Taking into consideration the protean manifestations of BD and the make up of the committee it was decided that each statement and recommendation should be voted on twice, once by everyone and once by those who considered themselves experts in the related discipline. Thus, each statement or recommendation received two votes during the second Delphi round.

RESULTS

The committee agreed on nine recommendations after two Delphi rounds (table 3).

All nine recommendations were accepted with good levels of agreement, with a mean score of ≥8.5. Furthermore there was excellent concordance between the level of agreement of the whole committee and the "experts in the field" (table 4).

Recommendations

1. Eye involvement

Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.

Eye involvement in BD follows a remitting and relapsing course and the recurrent inflammatory attacks result in irreversible damage and visual loss. Suppression of the inflammation and the prevention of recurrences of ocular attacks should be the goals. Azathioprine is widely accepted as the initial agent for ocular involvement of BD.

The placebo controlled randomised controlled trial (RCT),[5] showed that azathioprine 2.5 mg/kg/day decreased hypopyon uveitis attacks (number needed to treat (NNT) = 4), stabilised visual acuity and decreased the development of new eye disease (NNT = 2). Moreover, the 7-year follow-up of these patients showed that the beneficial effect of azathioprine continued in the long term.[6] The committee discussed a possible role for prophylactic treatment with azathioprine in patients carrying a high risk for developing eye disease such as young males. It was decided that more prospective data were needed.

Local and systemic corticosteroids for eye involvement, especially during attacks, are generally used with no evidence from RCTs. Corticosteroids rapidly suppress the inflammation but potential side effects including, cataracts and glaucoma, cause concern.

2. Refractory eye involvement

If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either ciclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively interferon (IFN)α with or without corticosteroids could be used.

In case of severe eye involvement another immunosuppressive needs to be added. Ciclosporine A 2–5 mg/kg/day shows its effect rapidly and is, here, usually the treatment of choice. There are three RCTs with ciclosporine A, showing a rapid and significant improvement in visual acuity,[7] and reducing the frequency and severity of ocular attacks.[8 9] Renal dysfunction was the most important adverse event. There are also a number of open studies with ciclosporine A showing salutary results.[10–24] Hypertension and nephrotoxicity are concerns.

As summarised in a recent position paper,[25] several open and retrospective studies and case reports[26–38] suggest that infliximab is a promising agent for refractory eye disease particularly in combination with other immunosuppressives. Although rapidly acting, relapses are common with stopping the solo use of infliximab. Due caution for tuberculosis, is important. The endemic areas for BD are also endemic for tuberculosis.[25]

Interferon α (IFNα), alone or in combination with corticosteroids appears to be a second choice in eye disease. The only RCT with IFNα, which included nine patients with mild uveitis,[39] and many open studies report beneficial results.[40–47] A review of literature suggested that IFNα2a seemed more effective than IFNα2b, but the number of patients who received IFNα2b was small.[48]

The committee discussed the possibility of using IFNα as a first line agent in some patients, but due to financial and safety concerns, mainly depression and cytopoenias, this was not recommended. IFNα should not be used in combination with azathioprine due to possible myelosuppression.[47]

3. Major vessel disease

There is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD, immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide or ciclosporine A are recommended. For the management of pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended.

The primary pathology leading to venous thrombosis in BD is the inflammation of the vessel wall. Systemic immunosuppressives are used to reduce this inflammation. However there are no RCTs directly addressing this issue. Nevertheless in the azathioprine trial,[6] the number of patients who developed thrombophlebitis was less in the azathioprine arm (NNT = 8). There is also one open trial with ciclosporine A, which showed beneficial results.[49] An abstract was discussed[50] that indicated that the risk for recurrent deep venous thrombosis and post-thrombotic syndrome was significantly lower in patients who were receiving immunosuppressives. Systemic immunosuppressives such as azathioprine 2.5 mg/kg/day may be prescribed for venous thrombosis of the extremities and monthly pulses of cyclophosphamide, a more potent immunosuppressive may be preferred for thrombosis of the superior vena cava or Budd–Chiari syndrome.

Peripheral artery aneurysms carry a high rupture risk and require surgical repair accompanied by systemic immunosuppressives. Retrospective case series and observational studies suggest that recurrences are less common in patients receiving immunosuppressives.[51–56]

Treatment of pulmonary aneurysms is mainly with immunosuppressives. Surgery carries a high risk of mortality. In emergencies, embolisation has been tried. Two series of patients with pulmonary artery aneurysms from the same unit were published 10 years apart. Early recognition and vigorous use of immunosuppressives with monthly pulses of cyclophosphamide and high dose corticosteroids have changed the prognosis of patients with pulmonary artery aneurysms.[57 58] Treatment with

Table 1 Categories of evidence

Category	Evidence
Ia	Meta-analysis of randomised controlled trials
Ib	Randomised controlled trial
IIa	Controlled study without randomisation
IIb	Quasi-experimental study
III	Non-experimental descriptive studies, such as comparative, correlation and case–control studies
IV	Expert committee reports or opinion or clinical experience of respected authorities or both

Table 2 Strength of recommendations

Strength	Based on
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

cyclophosphamide for at least 2 years, followed by azathioprine is recommended.

4. Anticoagulation

There are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD.

The venous thrombi in BD adhere to the vessel wall and do not result in emboli. Pulmonary embolism is rare despite a high frequency of venous thrombosis. Thus anticoagulants, antiplatelet or antifibrinolytic agents are not recommended. Another reason to avoid these agents is the possibility of a coexisting pulmonary arterial aneurysm, which might result in fatal bleeding. The previously quoted abstract showed that anticoagulants did not reduce the risk of recurrent venous thrombosis.[50] Controlled trials are needed.

5. Gastrointestinal involvement

There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement in BD. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists or thalidomide should be tried first before surgery, except in emergencies.

The gastrointestinal involvement of BD is characterised by single or multiple deep penetrating ulcers, mostly in the terminal ileum, the ileoceacal region and the colon. These deep penetrating ulcers tend to perforate, requiring emergency surgical procedures such as ileocolectomy or hemicolectomy with high recurrence and re-operation rates at long term. Except for such emergencies, medical treatment with immunosuppressives should be tried first. There are no controlled trials and retrospective studies suggest corticosteroids, sulfasalazine and azathioprine have been effective in obtaining remission without the need for surgery in many patients.[59 60] One study reported that azathioprine decreased re-operation rates and suggested that it should be used as maintenance therapy in patients who require surgery.[60] Finally there are case reports of successful use of TNFα antagonists and thalidomide in resistant and complicated cases.[61–65]

6. Joint involvement

In most patients with BD, arthritis can be managed with colchicine.

In BD, arthritis usually follows a mild and transient course usually without deformities or erosions. It mainly involves the large joints, such as the knees and ankles. Erosive changes are rare. Colchicine 1–2 mg/day is usually effective. Two RCTs tested the efficacy of colchicine in BD patients with arthritis[66 67] and both showed beneficial effects.

One RCT with benzathine penicillin[68] and open studies with indomethacine[69] and oxaprozin[70] showed some efficacy whereas azapropazone 900 mg/day was[71] and intramuscular depot corticosteroid[72] was not effective.

IFNα,[39 73] azathioprine[5] and TNFα blockers[74] may be tried in rare cases with resistant, longer lasting and disabling attacks.

7. Neurological involvement

There are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended.

Treatment choices in neurological disease depend mainly on anecdotal reports and experience. For parenchymal involvement

Table 3 Nine recommendations on Behçet disease (BD) that were developed after two anonymous Delphi rounds

No.	Recommendation
1	Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.
2	If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either ciclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively IFNα with or without corticosteroids could be used instead.
3	There is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide or ciclosporine A are recommended. For the management of pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended.
4	Similarly there are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD.
5	There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement of BD. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists and thalidomide should be tried first before surgery, except in emergencies.
6	In most patients with BD, arthritis can be managed with colchicine.
7	There are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended.
8	Ciclosporine A should not be used in BD patients with central nervous system involvement unless necessary for intraocular inflammation.
9	The decision to treat skin and mucosa involvement will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should be treated according to the dominant or codominant lesions present.
	Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers.
	Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient.
	Colchicine should be preferred when the dominant lesion is erythaema nodosum.
	Leg ulcers in BD might have different causes. Treatment should be planned accordingly.
	Azathioprine, IFNα and TNFα antagonists may be considered in resistant cases.

CNS, central nervous system; IFN, interferon; TNF, tumour necrosis factor.

Table 4 Category of evidence, strength of recommendations and level of agreement of recommendations

Recommendation no.	Category of evidence	Strength of recommendation	Level of agreement (VAS, mm)	
			Whole committee	Experts in the field
1 Eye involvement	Ib	A/D	9.57 (0.51)	9.73 (0.47)
2 Refractory eye involvement	Ib/IIb	C/D	8.71 (0.91)	8.9 (0.83)
3 Major vessel disease	III	C	8.64 (1.01)	8.88 (0.83)
4 Anticoagulation	IV	D	8.50 (1.74)	8.86 (1.46)
5 Gastrointestinal involvement	III	C	8.71 (0.47)	8.75 (0.46)
6 Joint involvement	Ib	A	9.0 (0.78)	8.89 (0.78)
7 Neurological involvement	III	C/D	8.50 (0.65)	8.44 (0.73)
8 Ciclosporine A neurotoxicity	III	C	8.79 (0.70)	8.78 (0.68)
9 Mucocutaneous involvement	Ib	A/C	9.07 (0.47)	9.11 (0.11)

Values are given as mean (SD) where appropriate.

high doses of pulsed corticosteroids, usually 3–7 pulses of intravenous methylprednisolone 1 mg/day, is given during attacks, followed by maintenance oral corticosteroids tapered over 2–3 months. Immunosuppressives may also be given to prevent recurrences and progression. There are two open successive studies involving a small number of patients with methotrexate from the same centre suggesting beneficial effects.[75 76]

Chlorambucil[77] is rarely used today due to high risk of serious adverse effects such as myelotoxicity and increased risk of malignancies. Azathioprine 2.5 mg/kg/day or in more severe cases monthly pulses of cyclophosphamide are preferred. IFNα and TNFα antagonists have been used with some success in resistant cases.[78–82] The treatment of dural sinus thrombosis presenting with increased intracranial pressure and headaches, is with brief courses of corticosteroids.

8. Ciclosporine A neurotoxicity

Ciclosporine A should not be used in patients with BD with central nervous system involvement unless necessary for intraocular inflammation.

Due to its potential neurotoxicity, ciclosporine A should not be the treatment of choice in patients with BD with neurological involvement, as three case–control studies have indicated.[83–85]

It has been suggested that ciclosporine A, itself neurotoxic, may potentiate central nervous system involvement.[84] A selection bias where more severe patients with eye disease receive ciclosporine A, among whom central nervous system disease is more common,[86] might also be operative. While it is best to avoid this drug in patients with neurological involvement, in patients with eye disease who cannot afford or tolerate other agents, ciclosporine A can still be used.

9. Mucocutaneous involvement

The decision to treat skin and mucosa involvement will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should be treated according to the dominant or codominant lesions present.

- Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers.
- Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient.
- Colchicine should be preferred when the dominant lesion is erythaema nodosum.
- Leg ulcers in BD might have different causes. Treatment should be planned accordingly.
- Azathioprine, IFNα and TNFα antagonists may be considered in resistant cases.

In skin mucosa disease treatment should be tailored according to how it affects the patients' quality of life. Oral ulcers may be managed by topical measures such as steroid preparations, lidocaine gel and chlorhexidine. Oral hygiene is important. Topical treatment of genital ulcers is difficult. Sucralfate suspension was shown to be effective for oral and genital ulcers in an RCT.[87]

For more resistant lesions systemic measures are needed. Colchicine is widely used without any solid proof of its efficacy except in erythaema nodosum lesions and genital ulcers among women.[66–88] Minocycline decreased the frequency of oral ulcers, erythaema nodosa and papulopustular lesions in an open study.[89]

Patients with resistant skin and mucosa findings can be treated with azathioprine, thalidomide, IFNα and in most resistant cases with TNFα antagonists. Azathioprine was also effective in preventing mucocutaneous lesions.[5] One RCT[90] and three open studies[91–93] showed that thalidomide was effective for oral and genital ulcers and papulopustular lesions in BD while an increase in the frequency of nodular lesions was reported. However, the potentially serious adverse events—especially teratogenicity and peripheral neuropathy that are sometimes permanent—limit its use. There is one RCT with etanercept[74] and one RCT[39] and several open studies[94–99] with IFNα showing that they produce significant improvement in mucocutaneous lesions. However they should only be used in selected cases considering their cost and potential side effects.

Leg ulcers in patients with BD may either be post-thrombotic, caused by venous stasis or vasculitic, caused by an inflammatory process. Management of the first type mainly consists of rest, elevation, topical zinc preparations and good hygiene with topical antibacterials when needed. For the second type systemic treatment is needed.

DISCUSSION

As with the other recommendations for various musculoskeletal disorders endorsed by EULAR,[100–108] these recommendations were formed by combining the best available evidence from the literature with the opinion of experts in BD. However, in contrast to previous projects, a second level of agreement was provided for each recommendation. This was derived from the votes of those members of the committee who felt they were "experts" particularly in the field regarding that recommendation. This approach makes us more confident in the final recommendations since there was excellent concordance between the level of agreement in the voting as a whole

committee or as experts in a particular field. This is important given the multisystem nature of the disease and the range of treating specialties.

In the earlier EULAR recommendations the quality of the studies was determined in accordance with scoring systems such as the Consolidated Standards of Reporting Trials (CONSORT) statement. This approach was abandoned during the development of more recent recommendations[106] as quality scores reflected the quality of reporting rather than the accuracy and credibility of the clinical trials. We also did not score the quality of the studies, but used the traditional hierarchy that depended on the type of study, although we acknowledge that this has limitations. According to this hierarchy, RCTs are considered to provide level Ib evidence, the second best evidence after meta-analysis. However recommendations should take into consideration the safety of treatment modalities as well as efficacy, and RCTs are usually not sensitive enough, often being too short or too small or too unrelated to the general population who will use the drug to consider evaluating for safety.[109]

The current set of recommendations focused primarily on management of established disease, leaving issues such as patient selection, initial management of early disease with the intention of preventing serious involvement, treatment strategies targeting particular disease mechanisms and monitoring to future projects. The refinements of tailoring treatment according to sex and age, commonly practiced since BD is known to follow a more severe course in young men, were not included in the body of the recommendations to prevent discrimination and misleading the health care providers.

The lack of controlled evidence, especially for vascular, neurological and gastrointestinal involvement, was pronounced. The recommendations related to these were mainly based on observational studies, retrospective analyses and clinical experience of the experts. Overall, only three of the recommendations were based on category Ib evidence, one was based on category II, three were based on category III and one was based on category IV evidence.

Finally, these evidence and expert opinion-based recommendations target many different clinical specialties and situations including primary care doctors, internists, rheumatologists, ophthalmologist, dermatologists, neurologists, surgeons and others involved in the care of patients with BD. Differences in health care systems, the economic status of different countries[110] and the burden some of the medications would bring were kept in mind while developing the recommendations. Like all recommendations, they have to be validated in different countries and different settings, also taking patient preferences into consideration, and they have to be expanded and updated as new treatment modalities are developed.

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