EULAR recommendations for the management of Behçet disease


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.

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 (GJ) 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. 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.
of agreement for each recommendation. Taking into consideration the protein 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 ≥ 0.5. 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), 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. 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, and reducing the frequency and severity of ocular attacks. Renal dysfunction was the most important adverse event. There are also a number of open studies with ciclosporine A showing salutary results. Hypertension and nephrotoxicity are concerns.

As summarised in a recent position paper, several open and retrospective studies and case reports 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.

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, and many open studies report beneficial results.

A review of literature suggested that IFNα2a seemed more effective than IFNα2b, but the number of patients who received IFNα2b was small.

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 cytopenias, this was not recommended. IFNα should not be used in combination with azathioprine due to possible myelosuppression.

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, 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.

An abstract was discussed 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.

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.
There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement of BD. Agents such as sulfasalazine, corticosteroids, azathioprine, cyclophosphamide, methotrexate, or TNFα antagonists have been effective in obtaining remission without surgery, except in emergencies. For the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD, controlled trials are needed. For dural sinus thrombosis corticosteroids are recommended.

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 2: Strength of recommendations

<table>
<thead>
<tr>
<th>Strength Based on</th>
<th>Category I evidence</th>
<th>Category II evidence or extrapolated recommendations from category I evidence</th>
<th>Category III evidence or extrapolated recommendations from category I or II evidence</th>
<th>Category IV evidence or extrapolated recommendations from category II or III evidence</th>
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### Table 3: Nine recommendations on Behcet disease (BD) that were developed after two anonymous Delphi rounds

<table>
<thead>
<tr>
<th>No.</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.</td>
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<tr>
<td>2</td>
<td>If the patient has severe eye disease defined as &gt;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.</td>
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<tr>
<td>3</td>
<td>There is no strong 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.</td>
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<tr>
<td>4</td>
<td>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.</td>
</tr>
<tr>
<td>5</td>
<td>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.</td>
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<tr>
<td>6</td>
<td>In most patients with BD, arthritis can be managed with colchicine.</td>
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<tr>
<td>7</td>
<td>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 and both showed beneficial effects.</td>
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<tr>
<td>8</td>
<td>One RCT with benzathine penicillin and open studies with indomethacin and oxaprozin showed some efficacy whereas azapropropazone 900 mg/day was and intramuscular depot corticosteroid was not effective.</td>
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<tr>
<td>9</td>
<td>IFNα,  azathioprine and TNFα blockers may be tried in rare cases with resistant, longer lasting and disabling attacks.</td>
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</table>

CNS, central nervous system; IFNα, interferon; TNFα, tumour necrosis factor.
Leg ulcers in BD might have different causes. Treatment should be selected according to the dominant lesion present. Colchicine should be preferred when the dominant lesion is erythema nodosum. Acne-like lesions are usually of cosmetic concern only. Thus, topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers. Colchicine is widely used without any solid proof of its efficacy except in erythema nodosum lesions and genital ulcers. However, the potentially serious adverse events—especially teratogenicity and peripheral neuropathy that are sometimes permanent—limit its use. There is one RCT with etanercept showing efficacy in preventing mucocutaneous lesions. One RCT and three open studies 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 and one RCT and several open studies 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 vasculitis, 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, 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 as quality scores reflected the quality of reporting rather than the accuracy and credibility of the clinical trials. We also did not score the trials because of the limited number of trials and the difficulty in comparing them.

REFERENCES


Recommendation


Quality & Safety in Health Care

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