



# 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,<sup>1,2</sup> 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 League Against Rheumatism (EULAR)'s standardised operating procedures,<sup>3</sup> 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.<sup>4</sup> 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  $\geq 8.5$ . 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),<sup>5</sup> 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.<sup>6</sup> 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) $\alpha$  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,<sup>7</sup> and reducing the frequency and severity of ocular attacks.<sup>8,9</sup> Renal dysfunction was the most important adverse event. There are also a number of open studies with ciclosporine A showing salutary results.<sup>10–24</sup> Hypertension and nephrotoxicity are concerns.

As summarised in a recent position paper,<sup>25</sup> several open and retrospective studies and case reports<sup>26–38</sup> 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.<sup>25</sup>

Interferon  $\alpha$  (IFN $\alpha$ ), alone or in combination with corticosteroids appears to be a second choice in eye disease. The only RCT with IFN $\alpha$ , which included nine patients with mild uveitis,<sup>39</sup> and many open studies report beneficial results.<sup>40–47</sup> A review of literature suggested that IFN $\alpha$ 2a seemed more effective than IFN $\alpha$ 2b, but the number of patients who received IFN $\alpha$ 2b was small.<sup>48</sup>

The committee discussed the possibility of using IFN $\alpha$  as a first line agent in some patients, but due to financial and safety concerns, mainly depression and cytopoenias, this was not recommended. IFN $\alpha$  should not be used in combination with azathioprine due to possible myelosuppression.<sup>47</sup>

**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,<sup>6</sup> 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.<sup>49</sup> An abstract was discussed<sup>50</sup> 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.<sup>51–56</sup>

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.<sup>57,58</sup> 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.<sup>50</sup> 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, TNF $\alpha$  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 ileocecal region and the colon. These deep

penetrating ulcers tend to perforate, requiring emergency surgical procedures such as ileocelectomy 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.<sup>59 60</sup> One study reported that azathioprine decreased re-operation rates and suggested that it should be used as maintenance therapy in patients who require surgery.<sup>60</sup> Finally there are case reports of successful use of TNF $\alpha$  antagonists and thalidomide in resistant and complicated cases.<sup>61-65</sup>

**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<sup>66 67</sup> and both showed beneficial effects.

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

IFN $\alpha$ ,<sup>39 73</sup> azathioprine<sup>5</sup> and TNF $\alpha$  blockers<sup>74</sup> 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, IFN $\alpha$ , azathioprine, cyclophosphamide, methotrexate and TNF $\alpha$  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 IFN $\alpha$ 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, TNF $\alpha$ 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, IFN $\alpha$ , azathioprine, cyclophosphamide, methotrexate and TNF $\alpha$ 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.<br>Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers.<br>Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient.<br>Colchicine should be preferred when the dominant lesion is erythema nodosum.<br>Leg ulcers in BD might have different causes. Treatment should be planned accordingly.<br>Azathioprine, IFN $\alpha$ and TNF $\alpha$ 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/Ib                | 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.<sup>75–76</sup>

Chlorambucil<sup>77</sup> 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. IFN $\alpha$  and TNF $\alpha$  antagonists have been used with some success in resistant cases.<sup>78–82</sup> 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.<sup>83–85</sup>

It has been suggested that ciclosporine A, itself neurotoxic, may potentiate central nervous system involvement.<sup>84</sup> A selection bias where more severe patients with eye disease receive ciclosporine A, among whom central nervous system disease is more common,<sup>86</sup> 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 erythema nodosum.
- ▶ Leg ulcers in BD might have different causes. Treatment should be planned accordingly.

- ▶ Azathioprine, IFN $\alpha$  and TNF $\alpha$  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.<sup>87</sup>

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

Patients with resistant skin and mucosa findings can be treated with azathioprine, thalidomide, IFN $\alpha$  and in most resistant cases with TNF $\alpha$  antagonists. Azathioprine was also effective in preventing mucocutaneous lesions.<sup>5</sup> One RCT<sup>90</sup> and three open studies<sup>91–93</sup> 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<sup>74</sup> and one RCT<sup>39</sup> and several open studies<sup>94–99</sup> with IFN $\alpha$  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,<sup>100–108</sup> 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<sup>106</sup> 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.<sup>109</sup>

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<sup>110</sup> 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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## REFERENCES

1. Yazici H, Tuzun Y, Pazarli H, Yurdakul S, Ozyazgan Y, Ozdogan H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. *Ann Rheum Dis* 1984;**43**:783–9.
2. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine (Baltimore)* 2003;**82**:60–76.

3. Dougados M, Betteridge N, Burmester GR, Euler-Ziegler L, Guillemain F, Hirvonen J, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;**63**:1172–6.
4. The AGREE Collaboration. Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. <http://www.agreecollaboration.org> (accessed 21 January 2007).
5. Yazici H, Pazarli H, Barnes CG, Tuzun Y, Ozyazgan Y, Silman A, et al. A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990;**322**:281–5.
6. Hamuryudan V, Ozyazgan Y, Hizli N, Mat C, Yurdakul S, Tuzun Y, et al. Azathioprine in Behçet's syndrome: effects on long-term prognosis. *Arthritis Rheum* 1997;**40**:769–74.
7. Ozyazgan Y, Yurdakul S, Yazici H, Tuzun B, Iscimen A, Tuzun Y, et al. Low dose cyclosporin A versus pulsed cyclophosphamide in Behçet's syndrome: a single masked trial. *Br J Ophthalmol* 1992;**76**:241–3.
8. Ben Ezra D, Cohen E, Chajek T, Friedman G, Pizanti S, de Courten C, et al. Evaluation of conventional therapy versus cyclosporine A in Behçet's syndrome. *Transplant Proc* 1988;**20**(3 Suppl 4):136–43.
9. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. *Lancet* 1989;**1**:1093–6.
10. Atmaca LS, Batioglu F. The efficacy of cyclosporin-a in the treatment of Behçet's disease. *Ophthalmic Surg* 1994;**25**:321–7.
11. Chavis PS, Antonios SR, Tabbara KF. Cyclosporine effects on optic nerve and retinal vasculitis in Behçet's disease. *Doc Ophthalmol* 1992;**80**:133–42.
12. Ermakova NA. Efficacy of corticosteroids and cyclosporin in the treatment of retinal vasculitis in patients with Behçet's disease. *Adv Exp Med Biol* 2003;**528**:563–5.
13. Fujino Y, Joko S, Masuda K, Yagi I, Kogure M, Sakai J, et al. Cyclosporin microemulsion pre-concentrate treatment of patients with Behçet's disease. *Jpn J Ophthalmol* 1999;**43**:318–26.
14. Hayasaka S, Kawamoto K, Noda S, Kodama T. Visual prognosis in patients with Behçet's disease receiving colchicine, systemic corticosteroid or cyclosporin. *Ophthalmologica* 1994;**208**:210–3.
15. Ozdal PC, Ortac S, Taskintuna I, Firat E. Long-term therapy with low dose cyclosporin A in ocular Behçet's disease. *Doc Ophthalmol* 2002;**105**:301–12.
16. Pacor ML, Biasi D, Lunardi C, Cortina P, Caramaschi P, Girelli D, et al. Cyclosporin in Behçet's disease: results in 16 patients after 24 months of therapy. *Clin Rheumatol* 1994;**13**:224–7.
17. Sajjadi H, Soheilian M, Ahmadi H, Hassanein K, Parvin M, Azarmina M, et al. Low dose cyclosporin-A therapy in Behçet's disease. *J Ocul Pharmacol* 1994;**10**:553–60.
18. Sullu Y, Oge I, Erkan D, Ariturk N, Mohajeri F. Cyclosporin-A therapy in severe uveitis of Behçet's disease. *Acta Ophthalmol Scand* 1998;**76**:96–9.
19. Whitcup SM, Salvo EC Jr, Nussenblatt RB. Combined cyclosporine and corticosteroid therapy for sight-threatening uveitis in Behçet's disease. *Am J Ophthalmol* 1994;**118**:39–45.
20. Nussenblatt RB, Palestine AG, Chan CC, Mochizuki M, Yancey K. Effectiveness of cyclosporin therapy for Behçet's disease. *Arthritis Rheum* 1985;**28**:671–9.
21. Muftuoglu AU, Pazarli H, Yurdakul S, Yazici H, Ulku BY, Tuzun Y, et al. Short term cyclosporin A treatment of Behçet's disease. *Br J Ophthalmol* 1987;**71**:387–90.
22. Wechsler B, Mertani EB, le Hoang P, de Groc F, Piette JC, Beaufils H, et al. Cyclosporin A is effective, but not safe, in the management of Behçet's disease. *Arthritis Rheum* 1986;**29**:574–5.
23. Diaz-Llopis M, Cervera M, Menezes JL. Cyclosporin A treatment of Behçet's disease: a long-term study. *Curr Eye Res* 1990;**9**(Suppl):17–23.
24. Binder AI, Graham EM, Sanders MD, Dinning W, James DG, Denman AM. Cyclosporin A in the treatment of severe Behçet's uveitis. *Br J Rheumatol* 1987;**26**:285–91.
25. Sfikakis PP, Markomichelakis N, Alpsoy E, Assaad-Khalil S, Bodaghi B, Gul A, et al. Anti-TNF therapy in the management of Behçet's disease – review and basis for recommendations. *Rheumatology (Oxford)* 2007;**46**:736–41.
26. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. *Arthritis Rheum* 2005;**52**:2478–84.
27. Sfikakis PP, Kaklamanis PH, Elezoglou A, Katsilambros N, Theodossiadis PG, Papaefthimiou S, et al. Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behçet disease. *Ann Intern Med* 2004;**140**:404–6.
28. Ohno S, Nakamura S, Hori S, Shimakawa M, Kawashima H, Mochizuki M, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. *J Rheumatol* 2004;**31**:1362–8.
29. Wechsler B, Sable-Fourtassou R, Bodaghi B, Huong DL, Cassoux N, Badelon I, et al. Infliximab in refractory uveitis due to Behçet's disease. *Clin Exp Rheumatol* 2004;**22**(4 Suppl 34):S14–6.
30. Abu El-Asrar AM, Abboud EB, Aldibhi H, Al-Arfaj A. Long-term safety and efficacy of infliximab therapy in refractory uveitis due to Behçet's disease. *Int Ophthalmol* 2005;**26**:83–92.
31. Arayssi T, Hamra R, Homeidan F, Uthman I, Awwad ST, Mroue K, et al. The efficacy of a single dose of infliximab in the treatment of Behçet's disease uveitis. *Clin Exp Rheumatol* 2005;**23**:427.

32. **Giansanti F**, Barbera ML, Virgili G, Pieri B, Emmi L, Menchini U. Infliximab for the treatment of posterior uveitis with retinal neovascularization in Behçet disease. *Eur J Ophthalmol* 2004;**14**:445–8.
33. **Lanthier N**, Parc C, Scavennec R, Dhote R, Brezin AP, Guillevin L. Infliximab in the treatment of posterior uveitis in Behçet's disease. Long term follow up in four patients. *Presse Med* 2005;**34**:916–8.
34. **Morris DS**, Gavin MP, Sturrock RD. The effect of anti-tumour necrosis factor  $\alpha$  (infliximab) on sight-threatening uveitis in a patient with Behçet's disease. *Adv Exp Med Biol* 2003;**528**:557–9.
35. **Munoz-Fernandez S**, Hidalgo V, Fernandez-Melon J, Schlincker A, Martin-Mola E. Effect of infliximab on threatening panuveitis in Behçet's disease. *Lancet* 2001;**358**:1644.
36. **Sayarlioglu M**, Cinal A, Topcu N, Demirok A. Effect of infliximab on refractory uveitis in Behçet's disease. *Ann Pharmacother* 2004;**38**:901–2.
37. **Sfikakis PP**, Theodosiadi PG, Katsiari CG, Kakkamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. *Lancet* 2001;**358**:295–6.
38. **Triolo G**, Vadala M, Accardo-Palumbo A, Ferrante A, Ciccio F, Giardina E, et al. Anti-tumour necrosis factor monoclonal antibody treatment for ocular Behçet's disease. *Ann Rheum Dis* 2002;**61**:560–1.
39. **Alpsoy E**, Durusoy C, Yilmaz E, Ozgurel Y, Ermis O, Yazar S, et al. Interferon  $\alpha$ -2a in the treatment of Behçet disease: a randomized placebo-controlled and double-blind study. *Arch Dermatol* 2002;**138**:467–71.
40. **Kotter I**, Vonthein R, Zierhut M, Eckstein AK, Ness T, Gunaydin I, et al. Differential efficacy of human recombinant interferon- $\alpha$ 2a on ocular and extraocular manifestations of Behçet disease: results of an open 4-center trial. *Semin Arthritis Rheum* 2004;**33**:311–9.
41. **Kotter I**, Zierhut M, Eckstein AK, Vonthein R, Ness T, Günaydin I, et al. Human recombinant interferon  $\alpha$ -2a for the treatment of with sight threatening posterior or panuveitis. *Br J Ophthalmol* 2003;**87**:423–31.
42. **Wechsler B**, Bodaghi B, Huong DL, Fardeau C, Amoura Z, Cassoux N, et al. Efficacy of interferon  $\alpha$ -2a in severe and refractory uveitis associated with Behçet's disease. *Ocul Immunol Inflamm* 2000;**8**:293–301.
43. **Bodaghi B**, Gendron G, Wechsler B, Terrada C, Cassoux N, Huong du LT, et al. Efficacy of interferon  $\alpha$  in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. *Br J Ophthalmol* 2007;**91**:335–9.
44. **Tugal-Tutkun I**, Guney-Tefekli E, Urgancioglu M. Results of interferon- $\alpha$  therapy in patients with Behçet uveitis. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:1692–5.
45. **Krause L**, Turnbull JR, Torun N, Pleyer U, Zouboulis CC, Foerster MH. Interferon  $\alpha$ -2a in the treatment of ocular Adamantiades-Behçet's disease. *Adv Exp Med Biol* 2003;**528**:511–9.
46. **Calguneri M**, Ozturk MA, Ertenli I, Kiraz S, Apras S, Ozbalkan Z. Effects of interferon  $\alpha$  treatment on the clinical course of refractory Behçet's disease: an open study. *Ann Rheum Dis* 2003;**62**:492–3.
47. **Hamuryudan V**, Ozyazgan Y, Fresko Y, Mat C, Yurdakul S, Yazici H. Interferon  $\alpha$  combined with azathioprine for the uveitis of Behçet's disease: an open study. *Isr Med Assoc J* 2002;**4**(11 Suppl):928–30.
48. **Kotter I**, Gunaydin I, Zierhut M, Stubiger N. The use of interferon  $\alpha$  in Behçet disease: review of the literature. *Semin Arthritis Rheum* 2004;**33**:320–35.
49. **Cantini F**, Salvarani C, Niccoli L, Padula A, Arena AI, Bellandi F, et al. Treatment of thrombophlebitis of Behçet's disease with low dose cyclosporin A. *Clin Exp Rheumatol* 1999;**17**:391–2.
50. **Kahraman O**, Celebi-Onder S, Kamali S, Inanc M, Ocal L, Aral O, et al. Long-term course of deep venous thrombosis in patients with Behçet's disease. In *Proceedings of the American College of Rheumatology 67th Annual Scientific Meeting, Orlando, Florida*. New Jersey, USA: Wiley, 2003; S385.
51. **Hosaka A**, Miyata T, Shigematsu H, Shigematsu K, Okamoto H, Ishii S, et al. Long-term outcome after surgical treatment of arterial lesions in Behçet disease. *J Vasc Surg* 2005;**42**:116–21.
52. **Tuzun H**, Besirli K, Sayin A, Vural FS, Hamuryudan V, Hizli N, et al. Management of aneurysms in Behçet's syndrome: an analysis of 24 patients. *Surgery* 1997;**121**:150–6.
53. **Nitecki SS**, Ofer A, Karram T, Schwartz H, Engel A, Hoffman A. Abdominal aortic aneurysm in Behçet's disease: new treatment options for an old and challenging problem. *Isr Med Assoc J* 2004;**6**:152–5.
54. **Park JH**, Chung JW, Joh JH, Song SY, Shin SJ, Chung KS, et al. Aortic and arterial aneurysms in Behçet disease: management with stent-grafts – initial experience. *Radiology* 2001;**220**:745–50.
55. **Kwon Koo B**, Shim WH, Yoon YS, Kwon Lee B, Choi D, Jang Y, et al. Endovascular therapy combined with immunosuppressive treatment for pseudoaneurysms in patients with Behçet's disease. *J Endovasc Ther* 2003;**10**:75–80.
56. **Le Thi Huong D**, Wechsler B, Papo T, Piette JC, Bletry D, Vitoux JM, et al. Arterial lesions in Behçet's disease. A study in 25 patients. *J Rheumatol* 1995;**22**:2103–13.
57. **Hamuryudan V**, Yurdakul S, Moral F, Numan F, Tuzun H, Tuzuner N, et al. Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. *Br J Rheumatol* 1994;**33**:48–51.
58. **Hamuryudan V**, Er T, Seyahi E, Akman C, Tuzun H, Fresko I, et al. Pulmonary artery aneurysms in Behçet syndrome. *Am J Med* 2004;**117**:867–70.
59. **Iida M**, Kobayashi H, Matsumoto T, Okada M, Fuchigami T, Yao T, et al. Postoperative recurrence in patients with intestinal Behçet's disease. *Dis Colon Rectum* 1994;**37**:16–21.
60. **Choi IJ**, Kim JS, Cha SD, Jung HC, Park JG, Song IS, et al. Long-term clinical course and prognostic factors in intestinal Behçet's disease. *Dis Colon Rectum* 2000;**43**:692–700.
61. **Lee JH**, Kim TN, Choi ST, Jang BI, Shin KC, Lee SB, et al. Remission of intestinal Behçet's disease treated with anti-tumor necrosis factor  $\alpha$  monoclonal antibody (Infliximab). *Korean J Intern Med* 2007;**22**:24–7.
62. **Kram MT**, May LD, Goodman S, Molinas S. Behçet's ileocolitis: successful treatment with tumor necrosis factor- $\alpha$  antibody (infliximab) therapy: report of a case. *Dis Colon Rectum* 2003;**46**:118–21.
63. **Hassard PV**, Binder SW, Nelson V, Vasilias EA. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease: a case report. *Gastroenterology* 2001;**120**:995–9.
64. **Travis SP**, Czajkowski M, McGovern DP, Watson RG, Bell AL. Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor  $\alpha$  antibody. *Gut* 2001;**49**:725–8.
65. **Brik R**, Shamali H, Bergman R. Successful thalidomide treatment of severe infantile Behçet disease. *Pediatr Dermatol* 2001;**18**:143–5.
66. **Aktulga E**, Altac M, Muftuoglu A, Ozyazgan Y, Pazarli H, Tuzun Y, et al. A double blind study of colchicine in Behçet's disease. *Haematologica* 1980;**65**:399–402.
67. **Yurdakul S**, Mat C, Tuzun Y, Ozyazgan Y, Hamuryudan V, Uysal O, et al. A double-blind trial of colchicine in Behçet's syndrome. *Arthritis Rheum* 2001;**44**:2686–92.
68. **Calguneri M**, Kiraz S, Ertenli I, Benekli M, Karaarslan Y, Celik I. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behçet's disease. A randomized clinical trial. *Arthritis Rheum* 1996;**39**:2062–5.
69. **Simsek H**, Dunder S, Telatar H. Treatment of Behçet disease with indomethacin. *Int J Dermatol* 1991;**30**:54–7.
70. **Takeuchi A**, Mori M, Hashimoto A, Chihara T. Efficacy of oxaprozin in the treatment of articular symptoms of Behçet's disease. *Clin Rheumatol* 1984;**3**:397–9.
71. **Moral F**, Hamuryudan V, Yurdakul S, Yazici H. Inefficacy of azapropazone in the acute arthritis of Behçet's syndrome: a randomized, double blind, placebo controlled study. *Clin Exp Rheumatol* 1995;**13**:493–5.
72. **Mat C**, Yurdakul S, Uysal S, Gogus F, Ozyazgan Y, Uysal O, et al. A double-blind trial of depot corticosteroids in Behçet's syndrome. *Rheumatology (Oxford)* 2006;**45**:348–52.
73. **Hamuryudan V**, Moral F, Yurdakul S, Mat C, Tuzun Y, Ozyazgan Y, et al. Systemic interferon  $\alpha$ 2b treatment in Behçet's syndrome. *J Rheumatol* 1994;**21**:1098–100.
74. **Melikoglu M**, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, et al. Short-term trial of enanercept in Behçet's disease: a double blind, placebo controlled study. *J Rheumatol* 2005;**32**:98–105.
75. **Hirohata S**, Suda H, Hashimoto T. Low-dose weekly methotrexate for progressive neuropsychiatric manifestations in Behçet's disease. *J Neurol Sci* 1998;**159**:181–5.
76. **Kikuchi H**, Aramaki K, Hirohata S. Low dose MTX for progressive neuro-Behçet's disease. A follow-up study for 4 years. *Adv Exp Med Biol* 2003;**528**:575–8.
77. **O'Duffy JD**, Robertson DM, Goldstein NP. Chlorambucil in the treatment of uveitis and meningocephalitis of Behçet's disease. *Am J Med* 1984;**76**:75–84.
78. **Nichols JC**, Ince A, Akduman L, Mann ES. Interferon- $\alpha$ 2a treatment of neuro-Behçet disease. *J Neuroophthalmol* 2001;**21**:109–11.
79. **Fujikawa K**, Aratake K, Kawakami A, Aramaki T, Iwanaga N, Izumi Y, et al. Successful treatment of refractory neuro-Behçet's disease with infliximab: a case report to show its efficacy by magnetic resonance imaging, transcranial magnetic stimulation and cytokine profile. *Ann Rheum Dis* 2007;**66**:136–7.
80. **Alty JE**, Monaghan TM, Bamford JM. A patient with neuro-Behçet's disease is successfully treated with etanercept: further evidence for the value of TNF $\alpha$  blockade. *Clin Neurol Neurosurg* 2007;**109**:279–81.
81. **Ribi C**, Sztajzel R, Delavelle J, Chizzolini C. Efficacy of TNF $\alpha$  blockade in cyclophosphamide resistant neuro-Behçet disease. *J Neurol Neurosurg Psychiatry* 2005;**76**:1733–5.
82. **Sarwar H**, McGrath H Jr, Espinoza LR. Successful treatment of long-standing neuro-Behçet's disease with infliximab. *J Rheumatol* 2005;**32**:181–3.
83. **Kotake S**, Higashi K, Yoshikawa K, Sasamoto Y, Okamoto T, Matsuda H. Central nervous system symptoms in patients with Behçet disease receiving cyclosporine therapy. *Ophthalmology* 1999;**106**:586–9.
84. **Kotter I**, Gunaydin I, Batra M, Vonthein R, Stubiger N, Fierlbeck G, et al. CNS involvement occurs more frequently in patients with Behçet's disease under cyclosporin A (CSA) than under other medications – results of a retrospective analysis of 117 cases. *Clin Rheumatol* 2006;**25**:482–6.
85. **Kato Y**, Numaga J, Kato S, Kaburaki T, Kawashima H, Fujino Y. Central nervous system symptoms in a population of Behçet's disease patients with refractory uveitis treated with cyclosporine A. *Clin Experiment Ophthalmol* 2001;**29**:335–6.
86. **Serdaroglu P**, Yazici H, Ozdemir C, Yurdakul S, Bahar S, Aktin E. Neurologic involvement in Behçet's syndrome. A prospective study. *Arch Neurol* 1989;**46**:265–9.
87. **Alpsoy E**, Er H, Durusoy C, Yilmaz E. The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. *Arch Dermatol* 1999;**135**:529–32.
88. **Mumcu G**, Ergun T, Elbir Y, Eksioğlu-Demiralp E, Yavuz S, Atalay T, et al. Clinical and immunological effects of azithromycin in Behçet's disease. *J Oral Pathol Med* 2005;**13**:14–6.
89. **Kaneko F**, Oyama N, Nishibu A. Streptococcal infection in the pathogenesis of Behçet's disease and clinical effects of minocycline on the disease symptoms. *Yonsei Med J* 1997;**38**:444–54.
90. **Hamuryudan V**, Mat C, Saip S, Ozyazgan Y, Siva A, Yurdakul S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;**128**:443–50.

91. **Gardner-Medwin JM**, Smith NJ, Powell RJ. Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behçet's disease: use of neurophysiological studies to detect thalidomide neuropathy. *Ann Rheum Dis* 1994;**53**:828–32.
92. **Saylan T**, Saltik I. Thalidomide in the treatment of Behçet's syndrome. *Arch Dermatol* 1982;**118**:536.
93. **Hamza MH**. Treatment of Behçet's disease with thalidomide. *Clin Rheumatol* 1986;**5**:365–71.
94. **Alpsoy E**, Yilmaz E, Basaran E. Interferon therapy for Behçet's disease. *J Am Acad Dermatol* 1994;**31**:617–9.
95. **Azizlerli G**, Sarica R, Kose A, Ovul C, Kavala M, Kayabali M, *et al*. Interferon  $\alpha$ -2a in the treatment of Behçet's disease. *Dermatology* 1996;**192**:239–41.
96. **Boyvat A**, Sisman-Solak C, Gurler A. Long-term effects of interferon  $\alpha$ 2A treatment in Behçet's disease. *Dermatology* 2000;**201**:40–3.
97. **Georgiou S**, Monastirli A, Pasmazi E, Gartaganis S, Goerz G, Tsambaos D. Efficacy and safety of systemic recombinant interferon- $\alpha$  in Behçet's disease. *J Intern Med* 1998;**243**:367–72.
98. **O'Duffy JD**, Calamia K, Cohen S, Goronzy JJ, Herman D, Jorizzo J, *et al*. Interferon- $\alpha$  treatment of Behçet's disease. *J Rheumatol* 1998;**25**:1938–44.
99. **Zouboulis CC**, Treudler R, Orfanos CE. Adamantiades-Behçet disease. Therapeutic administration of systemic recombinant interferon- $\alpha$ -2a. *Hautarzt* 1993;**44**:440–5.
100. **Bertsias GK**, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, *et al*. EULAR recommendations for the management of systemic lupus erythematosus (SLE). Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. Published Online First: 15 May 2007. doi:10.1136/ard.2007.070367
101. **Hellmich B**, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillemin L, *et al*. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2007;**66**:605–17.
102. **Zhang W**, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, *et al*. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;**66**:377–88.
103. **Zhang W**, Doherty M, Pascual E, Bardin T, Barskova V, Conaghan P, *et al*. EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006;**65**:1301–11.
104. **Zhang W**, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, *et al*. EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006;**65**:1312–24.
105. **Combe B**, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, *et al*. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;**66**:34–45.
106. **Zhang W**, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, *et al*. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2005;**64**:669–81.
107. **Jordan KM**, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, *et al*. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003;**62**:1145–55.
108. **Pendleton A**, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, *et al*. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2000;**59**:936–44.e.
109. **Yazici H**. Use and abuse of the controlled clinical trial. *Bull NYU Hosp Jt Dis* 2007;**65**:132–4.
110. **Sut N**, Seyahi E, Yurdakul S, Senocak M, Yazici H. A cost analysis of Behçet's syndrome in Turkey. *Rheumatology (Oxford)* 2007;**46**:678–82.

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