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ABSTRACT

Objectives: To present and analyse the literature sources regarding the management of Behçet disease (BD) identified during the systematic literature research, which formed the basis for the European League Against Rheumatism (EULAR) evidence-based recommendations for the management of BD.

Methods: Problem areas and related keywords regarding the management of BD were determined by the multidisciplinary expert committee commissioned by EULAR for developing the recommendations. A systematic literature research was performed using MedLine and Cochrane Library resources through to December 2006. Meta-analyses, systematic reviews, randomised controlled trials (RCTs), open studies, observational studies, case control studies and case series' involving ⩾5 patients were included. For each intervention the effect size and number needed to treat were calculated for efficacy. Odds ratios and numbers needed to harm were calculated for safety issues of different treatment modalities where possible.

Results: The literature research yielded 137 articles that met the inclusion criteria; 20 of these were RCTs. There was good evidence supporting the use of azathioprine and ciclosporin A in eye involvement and interferon (IFN)α in mucocutaneous involvement. There were no RCTs with IFNα or tumour necrosis factor (TNF)α antagonists in eye involvement. Similarly controlled data for the management of vascular, gastrointestinal and neurological involvement is lacking.

Conclusion: Properly designed, controlled studies (new and confirmatory) are still needed to guide us in managing BD.

The treatment of Behçet disease (BD) aims to suppress inflammation, and involves the use of immunosuppressives for treatment of serious organ-related issues such as ocular, vascular and neurological involvement. By contrast, the aim in the management of self-limiting manifestations such as skin mucosa and joint involvement is usually suppression of symptoms. The management of BD should be tailored according to the involved systems as well as age and sex, since BD follows a more severe course among young men.

The European League Against Rheumatism (EULAR) commissioned a task force to prepare recommendations for the management of BD. This exercise involved evidence-based and expert opinion-based approaches. The current review reports the results of the systematic literature research that formed the basis for these recommendations.[1]

METHODS

The systematic literature research was performed using the MedLine and Cochrane Library databases, between 1966 and December 2006. Due to the multisystemic nature of BD requiring different management approaches for each type of involvement, two search strategies were followed: (1) all pharmacological and surgical interventions determined by the committee were used with "Behcet" as index term and the index terms were exploded and (2) different types of involvement and lesions that were determined were searched with "Behcet" AND "treatment", with specific organ involvement as index terms exploded. The references of the selected articles were also manually searched for any relevant articles that were missed.

Inclusion/exclusion criteria

Articles in English, German, French, Turkish and Japanese were included. Meta-analyses, systematic reviews, randomised controlled trials (RCTs), open studies, observational studies, case control studies and case series' involving ⩾5 patients were included. Articles which were duplicates, narrative reviews, editorials and case reports were excluded, as were studies involving other diseases (such as other causes of uveitis) that did not report the results for patients with BD separately.

The best available evidence was used for evaluating the efficacy of an intervention. The categories of evidence were determined according to the traditional hierarchy (table 1). In contrast to what was evaluated for efficacy, evaluation of safety was not limited to the best available evidence but included RCTs as well as open, observational and retrospective studies. Only studies on pharmacological treatment are reported in this paper.

Statistical analysis

Because of a paucity of RCTs and different outcome parameters used, it was not possible to pool the results in a meta-analysis. The outcome parameter that was evaluated in each study was given separately. The effect size (ES) and 95%

Table 1 Categories of evidence

Category	Evidence
Ia	Meta-analysis of randomised controlled trials
Ib	Randomised controlled trial
IIa	Controlled study without randomisation
IIb	Quasiexperimental 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

confidence intervals (95% CI) were calculated for continuous parameters and the number needed to treat (NNT) was calculated for dichotomous parameters. Effect size for a particular parameter was calculated as (mean at the end−mean at entry)/SD of the mean at entry. It is considered "small" when <0.2 and "large" when it is >0.8. NNT is defined as the number of patients who must be treated in order to obtain benefit in one patient and is calculated as the reciprocal of the difference in the probabilities of an effect in treatment and control groups (1/(proportion of improvement in active treatment group−proportion of improvement in control group)).[2] Safety was evaluated using number needed to harm (NNH) for randomised controlled studies and odds ratios (ORs) for case control studies. NNH is defined as the number of patients who receive the active treatment that will lead to one additional patient being harmed compared with those receiving placebo and is calculated as 1/(proportion of event in active treatment group−proportion of event in placebo group). The number of patients who were withdrawn due to each specific adverse event was used when calculating NNH.

RESULTS

The literature search yielded 2402 citations, and 137 articles met the inclusion criteria. Of those 137, 20 were RCTs (table 2). The results are reported by therapeutic agent, different from the recommendations that were structured by organ or system involvement because most trials have multiple outcomes involving more than one system.

Azathioprine

There was only 1 RCT with azathioprine in 73 patients with and without eye involvement[3] (table 2). It showed that azathioprine decreased hypopyon uveitis attacks (NNT = 4; 95% CI 2.1 to 16.3) and preserved visual acuity (p = 0.025) when compared to placebo. Azathioprine also decreased the development of new eye disease among patients with BD without eye involvement (NNT = 2; 95% CI 1.2 to 4.4). Further, 7 years after the original study Hamuryudan *et al* showed that long term there was less blindness in the original azathioprine group (NNT = 4; 95% CI 1.9 to 43.9) and less development of new eye disease (NNT = 3; 95% CI 1.3 to 3.3).[4]

Azathioprine also decreased the development of new genital ulcers (NNT = 4; 95% CI 2.3 to 13.3), arthritis (NNT = 6; 95% CI 3.3 to 35.7) and thrombophlebitis (NNT = 8; 95% CI 2.1 to 30.3). Long term,[4] vascular and neurological involvement was less among patients who had been treated with azathioprine (NNT = 4; 95% CI 1.8 to 23.4).

Uncontrolled data suggest similar beneficial effects of azathioprine in gastrointestinal involvement[5] and in the long-term treatment of vascular involvement.

There were no withdrawals due to toxicity during the RCT with azathioprine. It was observed in an open study that concomitant use of azathioprine with interferon α (IFNα) could cause leukopoenia.[6]

Ciclosporin A

A single blind RCT compared 5 mg/kg/day of ciclosporin A with monthly pulses of cyclophosphamide.[7] Ciclosporin A produced a rapid and significant improvement in visual acuity when compared to cyclophosphamide during the first 6 months (ES = 1.06, (95% CI 0.15 to 1.89). This effect did not continue after 6 months. A second RCT compared ciclosporin A 5–10 mg/day with so-called "conventional treatment".[8] There was a marked improvement in ocular attacks (NNT = 4) over a period of 3 years. The third RCT compared ciclosporin A 10 mg/kg/day with colchicine 1 mg/day and showed that ciclosporin A provided significant improvement in the frequency and severity of ocular attacks.[9] One drawback of this study was that the dose of ciclosporin A used was very high.

An open trial with ciclosporin A in seven patients with venous thrombosis reported complete remission of thrombophlebitis within 2 months without residual venous insufficiency and no recurrences as long as treatment was continued.[10]

In the only RCT reporting adverse events in detail,[8] the NNH of ciclosporin A 10 mg/kg/day, was 45 for renal dysfunction. Among the 15 open studies with ciclosporin A in eye disease, all supporting its efficacy, 13 also provided data on safety (table 3).[11–25] Ciclosporin dose was between 2–10 mg/kg/day and the mean (SD) duration of treatment was 19.1 (16.2) months in these studies.

Three case-controlled studies have addressed neurotoxicity of ciclosporin A.[26–28] The odds ratio for developing serious neurological involvement was 9.9 (95% CI 3.9 to 25.2) (12/47 patients receiving ciclosporin A vs 9/270 receiving other drugs or no medication);[26] >79 (95% CI 7.9 to 620) (6/21 episodes under ciclosporin A vs 0/175 under other drugs);[27] and 6.8 (95% CI 0.8 to 60) (6/40 patients under ciclosporin A vs 0/60 under other drugs)[28] in these studies.

IFNα

There was one RCT with IFNα[29] (table 2). It showed significant improvement in the duration and pain of oral ulcers and the frequency of genital ulcers and papulopustular lesions. Complete remission was achieved in 2 of 23 patients receiving IFNα and in none of 21 patients receiving placebo (NNT = 12).

None of the patients were withdrawn from this study due to toxicity (table 4). Flu-like symptoms were observed in 78% of patients. A total of 14 open studies, involving 257 patients, provided information on toxicity[5 30–42] (table 4).

Tumour necrosis factor α (TNFα) antagonists

Infliximab

A position paper, based on open and retrospective experience, emphasised that infliximab may be a rapidly acting agent in patients with relapsing posterior uveitis inadequately controlled with other immunosuppressive.[43] The general opinion is that the response to treatment is rapid[44–46] decreasing the frequency of attacks and improving visual acuity[47] and that10 mg/kg might not be superior to 5 mg/kg in efficacy.[48] With regard to long-term efficacy (23 (7.4) months), repeated infusions are needed.[49]

Table 2 Randomised controlled trials

Intervention	No of patients	Duration	Outcome	Efficacy*	Toxicity†
Azathioprine (2.5 mg/kg) vs placebo (without eye disease)[3]	12 vs 13	2 years	New eye disease	NNT = 2 (1.2 to 4.4)	None
Azathioprine (2.5 mg/kg) vs placebo (with eye disease)[3]	25 vs 23	2 years	Hypopion uveitis	NNT = 4 (2.1 to 16.3)	None
Ciclosporin A 5 mg/kg/day vs cyclophosphamide 1 g/month intravenously[7]	12 vs 11	6 months	Frequency of attack	ES = −0.12	NS
			Visual acuity	ES = 1.06	
Ciclosporin 10 mg/day (later 5 mg/day) vs conventional therapy (prednisolone 1–1.5 mg/day or chlorambucil 0.1–0.2 mg/day[8]	20 vs 20	3 years	Prevention of marked worsening	NNT = 4 (1.8 to 20.7)	NNH = 20
Ciclosporin (10 mg/kg/day) vs colchicine (1 mg/day)[9]	47 vs 49	16 weeks	Frequency of ocular attack	p<0.001	Renal dysfunction, NNH = 47
			Severity of ocular attack	p<0.001	Hepatic dysfunction, NNH = 25
IFNα-2a (6 MU 3/7) vs placebo[29]	23 vs 21	3 months	Complete remission of mucocutaneous lesions	NNT = 12 (−2.82% to 20.21%)	None
Etanercept (25 mg 2/7) vs placebo[50]	20 vs 20	4 weeks	Oral ulcers	ES = 0.59 (0.05 to 1.22)	Diarrhoea, NNH = 20
			Genital ulcers	ES = 0.33 (0.3 to 0.94)	
			Papulopustular lesions	ES = 0.51(−0.13 to 1.13)	
			Nodular lesions	ES = 0.19 (−0.44 to 0.8)	
			Arthritis	ES = 0.24 (−0.38 to 0.86)	
Colchicine 1.5 mg/day vs placebo[57]	14 vs 14	6 months	Improvement in nodular lesions	NNT = 14 (−15.62% to 29.90%)	None
			Improvement in arthritis	NNT = 5 (−40.73% to 80.73%)	
Colchicine 1–2 mg/day vs placebo[58]	58 vs 58	2 years	Complete remission of oral ulcers	Women: NNT = 29 (−3.30% to 10.45%)	None
			Complete remission of genital ulcers	Women: NNT = 5 (−5.74% to 45.95%)	
			Complete remission of papulopustular lesions	Women: NNT = 27 (−8.20% to 15.87%)	
			Complete remission of nodular lesions	Women: NNT = 6 (−9.01% to 42.34%)	
				Men: NNT = 4 (6.23% to 53.77%)	
			Arthritis	Women: p = 0.014	
				Men: p = 0.026	
Thalidomide 100 mg vs placebo[62]	32 vs 32	24 weeks	Complete remission of mucocutaneous lesions	NNT = 16 (−2.14% to 14.64%)	Polyneuropathy, NNH = 32 (−2.90% to 9.15%)
Thalidomide 300 mg vs placebo[62]	31 vs 32	24 weeks	Complete remission of mucocutaneous lesions	NNT = 7 (3.4 to 31.4)	Polyneuropathy, NNH = 11 (−0.73% to 20.08%)
Benzathine penicillin 1.2 MU every 3 weeks+colchicine 1–1.5 mg vs colchicine 1–1.5 mg[66]	60 vs 60	2 years	Arthritis	ES = 0.52	None
Benzathine penicillin 1.2 MU every 3 weeks+colchicine 1–1.5 mg vs colchicine 1–1.5 mg[67]	94 vs 60	Not stated	Frequency of oral ulcers	ES = 0.35	
			Frequency of genital ulcers	ES = 0.17	
			Frequency of erythaema nodosa	ES = 0.25	
Acyclovir (5×800 mg for 1 week+2×400 mg for 11 weeks) vs placebo[71]	35 vs 35	3 months	Frequency of oral ulcers	p = 0.21	None
			Frequency of genital ulcers	p = 0.17	
Azopropazone 3×300 mg vs placebo[72]	28 vs 29	3 weeks	Arthritis	NNH = −9	NNH = 28
Methylprednisolone acetate 40 mg every 3 weeks vs placebo[75]	42 vs 44	27 weeks	Oral ulcers	p = 0.7	None
			Genital ulcers	p = 0.7	
			Papulopustular lesions	p = 0.5	
			Erythaema nodosum	p = 0.005	
			Arthritis	p = 0.9	
Acetazolamide 2×250 mg vs placebo[76]	29 vs 29	4 weeks (crossover)	Improvement in angiographic signs	NNT = 8 (3.8–174.9)	None
			Improvement in visual acuity	NNT = 11 (4.2 to 11.8)	
Rebamipide (300 mg/day) vs placebo[80]	19 vs 16	6 months	Frequency of oral ulcers	NNT = 4 (−4.86 to 62.84)	None
			Pain of oral ulcers	NNT = 5 (−12.62 to 56.32)	
Dapsone 100 mg/day vs placebo[81]	16 vs 4	3 months	Number of oral ulcers	ES = 0 (−0.88 to 0.88)	None

Continued

Table 2 Continued

Intervention	No of patients	Duration	Outcome	Efficacy*	Toxicity†
			Frequency of oral ulcers	ES = 1.79 (0.69 to 2.74)	
			Duration of oral ulcers	ES = 2.32 (1.11 to 3.33)	
			Number of genital ulcers	ES = 1.05 (0.08 to 1.94)	
			Frequency of genital ulcers	ES = 0.59 (−0.03 to 1.45)	
			Duration of genital ulcers	ES = 0.07 (−0.81 to 0.94)	
Transfer factor vs placebo (once)[82]	20 vs 20	6 months	Oral ulcer score	p>0.05	NS
Topical sucralfate four times a day vs placebo[92]	16 vs 14	3 months	Frequency of oral ulcers	ES = 0.71	None
			Pain of oral ulcers	ES = 1.23	
			Healing time of oral ulcers	ES = 0.81	
			Frequency of genital ulcers	ES = 0.27	
			Pain of genital ulcers	ES = 0.32	
			Healing time of genital ulcers	ES = 1.39	
IFNα-2c hydrogen 1×10^5 U/g vs placebo[93]	30 vs 31	24 weeks	Frequency of oral ulcers	p = not significant	NNH = 30

*Effect size (ES) was calculated for comparing continuous outcome parameters and number needed to treat (NNT) was calculated for comparing dichotomous outcome parameters. When sufficient data for calculating ES or NNT were not provided in the manuscript, p values, which were given in the manuscript, were used; †number needed to harm (NNH) was used for comparing withdrawals due to toxicity.
IFN, interferon.

Etanercept

The only RCT with a TNFα antagonist in BD was a 4-week placebo controlled etanercept trial, which involved 40 men with mucocutaneous involvement[50] (table 2). Not suppressing the pathergy reaction, etanercept decreased the frequency of oral ulcers, papulopustular lesions and arthritis with a moderate effect size, and the frequency of genital ulcers and nodular lesions with a small effect size. One patient in the etanercept arm was withdrawn from the study due to diarrhoea.

Cyclophosphamide

Currently the main use of cyclophosphamide in BD is in major vascular involvement. Two retrospective studies by Hamuryudan *et al* emphasised its role in treating pulmonary artery aneurysms. In the first report, which evaluated patients registered until 1992, 17 of 24 patients were treated with cyclophosphamide.[51] A total of 12 patients, 6 of whom had not had time to use immunosuppressives, had died after a mean (SD) of 9.5 (11) months after the onset of haemoptysis. In the second report, which evaluated patients registered from 1992 to 2003, 25 of 26 patients with a mean follow-up after the diagnosis of pulmonary artery aneurysms of 48.8 (41.4) months, were treated with cyclophosphamide and only 6 of them died.[52]

Table 3 Toxicity of ciclosporin A in open studies

Toxicity	No of patients (%)	Withdrawals due to toxicity
Renal dysfunction	56/242 (23)	9/56
Hypertension	28/242 (12)	1/28
Neurotoxicity	24/242 (10)	8/24
ALT/AST elevation	8/242 (3)	–
Hyperbilirubinaemia	8/242 (3)	–
Hyperuricaemia	3/242 (1)	–
Nausea	3/242 (1)	3/3

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Three of the open studies reported mild side effects such as leukopoenia, hair loss, anorexia and nausea.[53–55] One open study focused on sperm counts and haemorrhagic cystitis,[56] and showed that azospermia was present in 11of 15 patients and haemorrhagic cystitis in 5 of 46 patients treated with cyclophosphamide.

Colchicine

There were two RCTs with colchicine (table 2). The first study was a 6-month, placebo controlled study including 14 patients in each group.[57] Colchicine 1.5 mg/day was not effective for oral ulcers, genital ulcers and papulopustular lesions. It was suggested that colchicine might be effective for nodular lesions in some patients (NNT = 14). Colchicine improved arthralgia (NNT = 28, 95% CI −50.5 to 57.6), but did not significantly improve arthritis in this study.

In the second study, 116 patients were randomised to receive either colchicine 1–2 mg/day or placebo for 2 years and the data was separately analysed in men and women.[58] Colchicine did not improve oral ulcers or papulopustular lesions. Genital ulcers improved only in women (NNT = 5, 95% CI −5.7 to 46). Nodular lesions improved in both sexes (NNT = 6, 95% CI 29.1 to 42.3 for women and NNT = 4, 95% CI 1.9 to 16.0 for men). During the 2 years of the study, 91% of women and 86% of men in the colchicine arm and 64% of women and 56% of men in the placebo arm had no episodes of arthritis (NNT = 4, 95% CI 2.1 to 20.8 for women and NNT = 4, 95% CI 1.9 to 11.8 for men). The mean number of inflamed joints was also less among men and women receiving colchicine (2.8 (11) vs 4.4 (7.9), p = 0.026 in men and 0.3 (1.1) vs 2.4 (6.0), p = 0.014 in women).

Although results from RCTs, including the more recent ones, are disappointing, there are open studies[59] and clinical observations[60] that suggest that there might be a subgroup of patients with oral ulcers who might benefit from this treatment.

Colchicine was well tolerated with no withdrawals due to toxicity in the RCTs. Mild side effects such as gastrointestinal disturbances and hair loss have been reported in uncontrolled studies.[60 61]

Table 4 Toxicity of interferon (IFN)α in open studies

Toxicity	No of patients (%)	Withdrawals due to toxicity
Flu-like symptoms	231/257 (90)	–
Depression	7/257 (3)	3/7
Alopecia	15/257 (6)	2/14
Leucopenia	9/257 (4)	–
Thrombopenia	1/257 (0.4)	–
Injection site ulcers	1/257 (0.4)	1/1
Epileptic seizures	1/257 (0.4)	1/1
ALT/AST elevation	2/257 (0.8)	1/1

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Thalidomide

The single RCT with thalidomide showed that it is effective for oral and genital ulcers and papulopustular lesions in BD, while an increase in the frequency of nodular lesions was reported[62] (table 2).

Polyneuropathy was the only cause for withdrawal from the RCT. Paresthaesias, somnolence, nausea, vomiting and skin rash were reported in few patients from open studies.[63–65]

Antibiotics, antivirals

There were two RCTs with benzathine penicillin[66 67] (table 2). In the first of these all 120 patients also received colchicine 1–1.5 mg/day and half were additionally randomised to receive benzathine penicillin 1.2 MU every 3 weeks.[66] At the end of 2 years, benzathine penicillin had a moderate effect size in preventing arthritis episodes. In the other study, which had a similar design, patients using penicillin and colchicine had small to moderate effect sizes for the improvement in mucocutaneous lesions, when compared to those receiving only colchicines.[67] Other antibiotics such as minocycline[68] and azithromycin,[69] and an antihelminthic drug, levamisole,[70] have been shown to provide some benefit.

The only antiviral studied in an RCT was acyclovir, which showed no effect[71] (table 2).

Non-steroidal anti-inflammatory drugs (NSAIDs)

In the only RCT with an NSAID, azapropazone 900 mg/day or placebo was given for 3 weeks to patients with BD with acute arthritis of less than 10 days duration[72] (table 2). Although the visual analogue scale reading for pain during the first week was less in the azapropazone group, at the end of 3 weeks arthritis persisted in 15 of 28 patients in the azapropazone group (53.5%) and 12 of 29 patients in the placebo group (41.3%). Moreover the decrease in pain was not associated with a decrease in the tender joint score.

In an open study, arthritis recovered in 24 of 30 patients treated with indomethacin.[73] In another open study involving five patients treated with oxaprozin pain and swelling decreased in four of the patients, three of whom had received concomitant corticosteroids.[74]

Corticosteroids

There was one placebo-controlled RCT with intramuscular depot corticosteroid (40 mg methylprednisolone acetate) injections every 3 weeks for 27 weeks[75] (table 2). There was no improvement in mucocutaneous lesions except for nodular lesions in this study. Although this study was adequately powered to show a difference of 30% with a significance level of 0.05 at a power of 80%, the number of patients with arthritis was quite small in each group and the mean number of arthritis episodes was not significantly different between the corticosteroid and placebo groups. The low dose of the corticosteroid used could have been another factor for the negative results observed.

Other pharmacological measures

One RCT with acetazolamide[76] and open studies and observational reports with tacrolimus[77 78] and methotrexate[79] showed some benefit for eye involvement.

There were three other RCTs involving patients with BD with mucocutaneous involvement (table 2). Rebamipide 300 mg/day decreased the number of oral ulcers and the pain caused by them.[80] Dapsone lessened the frequency and duration of oral ulcers and the number and frequency of genital ulcers.[81] Transfer factor was not effective for any of the manifestations of BD.[82] It was suggested in an open study that oral zinc sulphate may be effective for BD.[83]

Open studies with chlorambucil have shown some efficacy for eye[84–88] and neurological involvement,[89] however serious toxicities such as leukopoenia and thrombocytopoenia were observed. Another major drawback is the increased risk of malignancies.

Two open successive studies evaluated the efficacy of methotrexate in a small number of patients with neurological involvement. In the first study, in which patients were followed for 12 months, there were six patients[90] and in the extension study another four patients were added and treated for up to 4 years.[91] The authors concluded that methotrexate may stabilise disease progression, however patients experienced exacerbations after they stopped treatment.

Topical measures

Sucralfate suspension has been used in a placebo-controlled RCT and was found effective in improving the frequency, healing time and pain of oral ulcers and the healing time of genital ulcers, but less so in improving the frequency and pain of genital ulcers[92] (table 2). The other RCT with a topical agent, IFNα-2c hydrogel 1×10^5 U/g showed that this regimen was not effective for oral ulcers, in contrast to a former study by the same group using IFNα-2c 1×10^6 U/g.[93] Another open study with topical ciclosporin A showed that ciclosporin A with a dose of 70 mg/g orobase was not effective for oral ulcers.[94]

DISCUSSION

The systematic literature research showed that until December 2006 there were only 20 RCTs on the management of patients with BD. There are no studies relating to the management of gastrointestinal and neurological involvement in BD. Another problem that has not been adequately addressed in an RCT or detailed and comprehensive observational study is whether anticoagulation is required for the venous thrombosis in BD. There were also no proper RCTs with IFNα for eye involvement. RCTs comparing IFNα, ciclosporin A and infliximab are also needed.

Withdrawal studies, which are sometimes a good way of showing efficacy, are also lacking in BD. A withdrawal study with colchicine is needed in particular due to the controversial and disagreeing results between RCTs and observational studies.

A limitation of this literature review was that the outcome parameters of different studies were not consistent, making it difficult to compare the results of different studies and impossible to pool the results for calculating the effect size of

treatment modalities. Another problem was the small number of RCTs available, compared to the many case series studies, which may be particularly misleading in a disease that follows a relapsing and remitting course. A good example of this in BD is with eye involvement where visual acuity drops during each uveitis attack, but may improve with time even without treatment. Accordingly, when the efficacy of a drug is evaluated by comparing the visual acuity during the attack to the visual acuity some time later, an improvement may be noted even if the drug is ineffective.

Studies related to surgical interventions are beyond the scope of this paper and are not included here. Similarly, questions related to treatment of early disease and the management of specific subgroups such as the young and male patients were not addressed and not included in the literature research. This review has pointed to gaps in our current knowledge and emphasises the need for further prospective RCTs in better managing Behçet disease.

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