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Pharmacotherapy for Behcet's syndrome (Review)

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[Intervention Review]

Pharmacotherapy for Behcet's syndrome

Antonio Saenz¹, Monica Ausejo², Beverley Shea³, George A Wells⁴, Vivian Welch⁵, Peter Tugwell⁵

¹Centro de Salud Pozuelo 1, INSALUD - Madrid, Pozuelo de Alarcón, Spain. ²Servicio de Farmacia Atencion Primaria Area, Madrid, Spain.

³Institute of Population Health, University of Ottawa, Ottawa, Canada. ⁴Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, Canada. ⁵Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, Canada

Contact address: Beverley Shea, Institute of Population Health, University of Ottawa, 1 Stewart St., Room 312, Ottawa, Ontario, K1N 6N5, Canada. bevshea@uottawa.ca.

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ABSTRACT

Background

Behcet's syndrome is a multisystemic disorder presenting with recurrent oral and genital ulcerations as well as ocular involvement. Treatment of Behcet's syndrome is symptomatic and empirical.

Objectives

To determine the effects of available pharmacological interventions in treating the different clinical features of Behcet's syndrome.

Search methods

We searched the Cochrane Musculoskeletal Group's trials register, the Cochrane Controlled Trials Register, and Medline up to January 1998. The computer search was complemented by a hand search of all bibliographic references from the reference lists of included trials. Principal investigators were contacted to seek unpublished literature. All languages were included.

Selection criteria

Studies were eligible if they fulfilled all of the four following criteria:

1. Randomized controlled trials, single or double-blind;
2. Participants were patients with Behcet's Syndrome as defined by the International Study Group, 1990 (Int Study Group 1990);
3. Interventions included any pharmacological therapy compared to placebo or some other pharmacological intervention for the treatment of Behcet's syndrome.
4. Outcome measures included active ocular inflammatory processes, arthritis, mucocutaneous manifestations (oral ulcer, genital ulcer, erythema nodosum), laboratory changes and major events such as adverse effects and death.

Data collection and analysis

The 32 potentially relevant references were assessed by two independent reviewers (MA, AS) according to the inclusion criteria. Ten trials fit the inclusion criteria and were included in this review. From the 10 included trials, data were independently extracted by the same two observers and cross checked. The quality of the included trials was assessed independently by two observers (MA, AS) using a validated scale (Jadad 1996).

For dichotomous measures, the treatment effect for each trial was calculated using a fixed effect model [Peto model (Petitti 1994)]. The weighted mean differences were based, if available, on end-of-trial results. The analysis was conducted separately for each different intervention. Since the trials could not be pooled it was not possible to carry out a sensitivity analysis by quality scores or a subgroup

analysis by drug dosages. Because of this lack of comparability across trials and the small number of trials, we could not conduct a heterogeneity test or a funnel plot.

Main results

Ten trials and 679 patients were included. There is insufficient evidence either to support or to refute some of the classic treatments for Behcet's syndrome, including colchicine, cyclophosphamide and steroids for eye involvement, azapropazone and colchicine for arthritis and acyclovir, colchicine and topical interferon for aphthas. The results confirm the protective effects of cyclosporine and azathioprine for eye involvement and benzathine-penicillin for arthritis.

Authors' conclusions

We conclude that further randomized, placebo-controlled, double-blind trials should be carried out to compare cyclosporine, azathioprine and benzathine-penicillin versus placebo in order to make the results generalizable and comparable.

PLAIN LANGUAGE SUMMARY

Pharmacotherapy for Behcet's syndrome

Behcet's syndrome is a multisystemic disorder presenting with recurrent oral and genital ulcerations as well as ocular involvement. Treatment of Behcet's syndrome is symptomatic and empirical.

Ten trials and 679 patients were included. There is insufficient evidence either to support or to refute some of the classic treatments for Behcet's syndrome, including colchicine, cyclophosphamide and steroids for eye involvement, azapropazone and colchicine for arthritis and acyclovir, colchicine and topical interferon for aphthas. The results confirm the protective effects of cyclosporine and azathioprine for eye involvement and benzathine-penicillin for arthritis.

We conclude that further randomized, placebo-controlled, double-blind trials should be carried out to compare cyclosporine, azathioprine and benzathine-penicillin versus placebo in order to make the results generalizable and comparable.

BACKGROUND

Behcet's syndrome is a multisystemic disorder presenting with recurrent oral and genital ulcerations as well as ocular involvement. In 1990, an international study group proposed standardized diagnostic criteria for Behcet's syndrome as follows: recurrent oral ulceration plus two of recurrent genital ulceration, eye lesions, skin lesions or pathergy test. The disease has a worldwide distribution with a prevalence ranging from 1:10,000 in Japan to 1:500,000 in Western countries. It affects mainly young adults ([Int Study Group 1990](#)).

It is considered an autoimmune disease since vasculitis is the main pathologic lesion and circulating autoantibodies to human oral mucous membrane are found in approximately 50 percent of cases. Familial occurrence has been reported, and in patients from Eastern Mediterranean countries and Japan, the disease appears to be linked to HLA-B5 and HLA-DR5 alloantigens.

The oral recurrent aphthous ulcerations are usually painful, persist for one to two weeks and subside without leaving scars. Gastrointestinal involvement includes mucosal ulcerations of the gut. The genital ulcers resemble the oral ones. Skin involvement includes folliculitis, erythema nodosum or an acne-like exanthem. However, vasculitis is uncommon. Nonspecific skin inflammatory reactivity to scratches or intradermal saline injection (pathergy test) is a common and specific manifestation in Japanese and Eastern Mediterranean patients.

Eye involvement is the most dreaded complication, since it occasionally progresses rapidly to blindness. Eye involvement in Behcet's syndrome includes iritis, posterior uveitis, hypopyon uveitis, retinal vessel occlusions and optic neuritis.

The arthritis of Behcet's syndrome is not deforming. It can sometimes affect the knees and ankles. Superficial or deep peripheral vein thrombosis is seen in one fourth of the patients. Although pulmonary emboli is a rare complication, the superior vena cava is sometimes obstructed. Pulmonary artery vasculitis has been reported in 5 percent of patients ([Moutsopoulos 1994](#)).

Central nervous system involvement includes benign intracranial hypertension, a multiple sclerosis-like picture, pyramidal involvement and psychiatric disturbances. Laboratory findings are mainly nonspecific indices of inflammation, although antibodies to human oral mucosae are also found. The severity of Behcet's syndrome abates with time. Apart from the cases with neurologic complications, life expectancy is usually unaffected, and the only serious complication is blindness.

Treatment of Behcet's syndrome is symptomatic and empirical. Topical corticoids have been used for mucous membrane involvement, rest and analgesics for arthritis, aspirin and dipyridamol for thrombophlebitis, and colchicine for mild forms of the syndrome. Systemic corticosteroid therapy and azathioprine or cyclosporine have been used for uveitis and central nervous system involvement.

With the emergence of new evidence in the last few years, there is a need for a systematic review to help guide clinicians in their treatment of these patients.

OBJECTIVES

To determine the efficacy of available pharmacological interventions in treating the different clinical features of Behcet's syndrome. These clinical features include active ocular inflammatory processes, hearing loss, arthritis, mucocutaneous manifestations, laboratory and major events such as death and adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were eligible if they fulfilled all of the following criteria: randomized controlled trials, single or double-blind. Open studies (with no blinding) were excluded.

Types of participants

Patients with Behcet's syndrome as defined by the International Study Group ([Int Study Group 1990](#)).

Types of interventions

Any pharmacological therapy compared to placebo or another pharmacological intervention for the treatment of Behcet's syndrome.

Types of outcome measures

The outcomes assessed for this meta-analysis are:

- 1.- Active ocular inflammatory processes (uveitis, hypopyon)
Frequency, severity, remission, partial improvement, deterioration
Withdrawals due to eye disease
Development of new eye disease
Corticoid treatment of deteriorating eye disease
Visual acuity change
Involvement of previously unaffected eye
- 2.- Arthritis
Number of arthritis attacks per person.
Number of episodes of arthritis attacks per group
Duration of episode
Severity of attack
Pattern of joint involvement
Necessity of corticosteroid treatment, either oral or enteral
- 3.- Mucocutaneous manifestations (oral ulcer, genital ulcer, erythema nodosum).
Frequency, number, duration, severity
- 4.- Laboratory changes in:
White cell counting (WCC)
C reactive protein (CRP)
Erythrocyte sedimentation rate (ESR)
- 5.- Hearing loss.
Change in dB hearing levels
- 6.- Major events such as adverse effects and death

Search methods for identification of studies

To identify trials of any pharmacological intervention versus either placebo or another pharmacological intervention for the management of the Behcet's syndrome, a search in the MEDLINE database was performed, from January 1966 to January 1998. The strategy used was the one developed by the Cochrane Collaboration, adopted and modified for the Cochrane Musculoskeletal Group ([Dickersin 1994](#)), as shown in [Appendix 1](#).

The reviewers processed the former 480 full references (authors, title, source, keywords, abstract, MeSH and keywords) to identify any potentially relevant articles. After discarding papers dealing with editorials, comments, reviews, either basic or animal research, diagnostics approach, follow-up studies, and case series, 27 references which included the words random, blinding, masking, trial or prospective study were initially included.

Two additional references were found in the Cochrane Controlled Trials Register (CCTR). The computer search was complemented by a hand search of all bibliographic references from the reference lists of included trials. Three additional references were included after this handsearching. Principal investigators were contacted to seek unpublished literature. All languages were included.

Finally, 32 references were included as potentially relevant.

Data collection and analysis

The Cochrane Controlled Trials Register (CCTR) will be searched for future updates.

The 32 potentially relevant references were assessed by two independent reviewers (MA, AS) according to five inclusion criteria: diagnosis of Behcet's syndrome, randomization, blinding, pharmacological treatment versus either placebo or another pharmacological treatment and measurement of a clinical outcome. Ten trials fit the inclusion criteria and were included in this review.

The 22 discarded references were excluded because they were: open studies (10 studies), follow-up studies (2), retrospective studies (2), uncontrolled (3), comments of a trial (2), patients with Behcet's syndrome included in a group with other non-Behcet's patients with uveitis and it was not possible to extract individual data (1), Behcet's patients were used to validate a questionnaire for Rheumatoid Arthritis (1) and a review of the disease (1).

Data extraction

From the 10 included trials, data were independently extracted by two observers (MA, AS) and cross-checked. The studies examined several different pharmacological interventions. In some cases two trials on the same intervention were found, but the data included different clinical outcomes, such as arthritis in one trial and mucocutaneous symptoms in another.

Because of the differences in interventions and outcomes across trials, it was not possible to pool data from different studies for any outcomes or interventions. This reflects a lack of standardization of outcomes measured for clinical trials examining Behcet's syndrome. It also demonstrates a need for further research, with standardized outcomes, so that larger numbers of patients are available for analysis.

To assess changes in disease activity, the following measurements were considered a priority: uveitis attacks, visual acuity changes, hearing changes, oral or genital ulcers count, swollen joint count, tender joint count, arthritis attacks and episodes per patient, episodes by group and pain.

Statistical analysis:

Since the different pharmacological interventions could not be pooled, they were analyzed separately. For dichotomous measures, the treatment effect for each trial was calculated using a fixed effect model [Peto model (Petitti 1994)].

The trials included in this review used different indices to evaluate changes in disease activity. For instance, different total numbers of joints were considered and assessments were measured with various scales. To enhance future comparability across trials all the continuous outcome variables were compared using standardized mean differences between intervention and placebo groups. The standardized mean differences were based, if available, on end-of-trial results.

One author (Ertenli) was contacted to determine if one trial ([Calguneri 1996a](#)) was masked, as well as to seek unpublished studies. As of March 1998, we have not received a reply. The estimates were calculated using Revman 3.01. The analysis was conducted separately for each different intervention, for the reasons described previously.

Since the trials could not be pooled it was not possible to carry out a sensitivity analysis by quality scores or a subgroup analysis by drug dosages. Because of this lack of comparability across trials and the small number of trials, we could not conduct a heterogeneity test or a funnel plot.

RESULTS

Description of studies

A total of 10 out of 32 potentially relevant references were included since they were randomized, controlled, single or double-blind trials ([Aktulga 1980](#), [Benamour 1991](#), [Benezra 1988](#), [Calguneri 1996a](#), [Davies 1988](#), [Hamuryudan 1991](#), [Masuda 1989](#), [Moral 1995](#), [Oryazgan 1992](#), [Yacizi 1990](#)).

All 10 RCTs included in the analysis assessed several clinical outcomes, some also reported side effects. In [Yacizi 1990](#), one of the patients on placebo died due to Behcet's-related pulmonary vascular disease. No other cases of death were reported in these trials.

Risk of bias in included studies

The quality of the included trials was assessed independently by two observers (MA, AS) using a validated scale ([Jadad 1996](#)). This scale consists of three items pertaining to the description of randomization, blinding, dropouts and withdrawals per group, as described in the report of a RCT. The scale ranges from zero to five (two points each for randomization and blinding and one point for the description of drop-outs and withdrawals per intervention group), with higher scores indicating superior reporting. Interobserver agreement was measured using a weighted kappa, an adjusted measure of agreement, removing contributions expected by chance. Values between 0.60-0.80

indicate substantial strength of agreement, higher than 0.81 is almost perfect ([Landis 1977](#)).

The interobserver agreement, before consensus, measured with kappa was equal to 0.71. Discussion resolved disagreements. The median quality score of the included trials was 3 (range 0-5).

The allocation concealment of the included trials was assessed independently by two observers (MA, AS). The allocation concealment was adequate in 2 trials, inadequate in 3 trials and unclear in 5 trials.

Effects of interventions

Ten trials out of 32 potentially relevant articles were included in this systematic review.

Overall, the included trials reported on 679 patients, of which 189 were randomized to a placebo group (22 patients from a cross-over design), 126 to colchicine, 104 to cyclosporine, 60 to colchicine plus benzathine-penicillin, 50 to a saliva autologue, 37 to azathioprine, 30 to azapropazone, 30 to topical alpha-interferon, 22 to acyclovir (cross-over design), 20 to conventional therapy (steroids, lekeran) and 11 to cyclophosphamide.

The results of the studies are summarized by four main categories: eye involvement, oral and genital ulcers, dermic lesions and arthritis. No studies explored changes in hearing.

Eye involvement:

In [Aktulga 1980](#), there were no differences in eye improvement between colchicine vs placebo with an odds ratio (OR) of 0.47 (95% CI: 0.06, 3.78).

In [Benezra 1988](#) (cyclosporine vs conventional therapy), the authors report that most of the patients on cyclosporine demonstrated better visual acuity after treatment. However, there was no difference in visual acuity after 1 month between cyclosporine and conventional therapy [WMD 0.070, (95%CI, -0.117, 0.257)]. After two years of receiving cyclosporine, most patients continue to show stable or better visual acuity than baseline, but there was no difference between cyclosporine and conventional therapy [WMD 0.120, (95%CI, -0.163, 0.403)].

In [Masuda 1989](#), cyclosporine resulted in significantly more improvements than colchicine in the frequency (OR 0.10, 95%CI, 0.04, 0.23) and severity (OR 0.10, 95%CI, 0.04, 0.23) of ocular attacks ($p < 0.001$ according to the authors). Clinical symptoms were significantly better in the cyclosporine group than in colchicine with an OR of 0.11 (95%CI, 0.03, 0.40, $p < 0.001$).

In [Oryazgan 1992](#), (low dose cyclosporine vs cyclophosphamide) the mean dose of cyclosporine used was 4.89 mg/kg/day during the 6 months of the masked period. Visual acuity significantly improved ($p < 0.0001$) when compared with that observed at entry, according to the authors. However, there was no difference between cyclosporine and cyclophosphamide [WMD 0.800 (95%CI, -2.521, 4.121)]. This initial improvement however disappeared by the time the trial was unmasked. The visual acuity among the 8 patients continuing to use cyclosporine at the end of the 24 months remained approximately the same at the time of unmasking of the trial or at entry. No change in visual acuity among the patients using cyclophosphamide occurred at the three time points, apart from

a trend to deterioration at the time of unmasking the trial when compared with that at the time of entry. Although there was a trend for fewer ocular attacks in the cyclosporine group, this did not reach statistical significance for the time intervals assessed with an WMD at 6 months of -0.140 (95%CI -0.350, 0.070) and 12 months [WMD -0.110 (95%CI -0.561, 0.341)].

In [Yacizi 1990](#), (azathioprine vs placebo) there were two different groups: with and without previous eye involvement. In the group without previous eye involvement, 9 patients were diagnosed with eye disease during the trial, 8 of 13 receiving placebo and 1 out of 12 receiving azathioprine [OR 0.11 (95% CI, 0.02, 0.54), $p = 0.008$ Fisher's exact test]. One patient receiving placebo required an injection of methylprednisolone to treat deteriorating eye disease.

In the group with previous eye involvement, 6 out of 23 patients receiving placebo were withdrawn because of severe eye disease compared to 0 of 25 azathioprine patients [OR 0.10 (95%CI, 0.02, 0.53)]. Fourteen patients had unocular eye disease at the start of the trial, 7 receiving azathioprine and 7 placebo. In 5 in the placebo group and 0 in the azathioprine group, disease developed in the unaffected eye [OR 0.06 (95%CI, 0.01, 0.46, $p < 0.001$)].

Seven patients taking placebo had 15 episodes of hypopyon uveitis as compared with one taking azathioprine who had a single episode [OR 0.16 (95% CI, 0.03, 0.70)]. This reached statistical significance in the trial ($p = 0.018$ Fisher's exact test). High dose methylprednisolone was required by 6 patients (with 9 episodes) taking azathioprine and 10 patients (with 16 episodes) taking placebo [OR 0.42 (95%CI, 0.13, 1.39)].

With data included on the six patients withdrawn from the trial because of severe eye disease, the mean visual acuity was unchanged between the first and last visits in the azathioprine group compared to a small but significant deterioration in visual acuity in the placebo group [WMD -0.910 (95% CI, -1.962, 0.142), $p < 0.025$]. The worsening in the placebo group was also evident when data on the six patients who were withdrawn were excluded from the analysis ($p < 0.01$).

Oral and genital ulcers :

In [Aktulga 1980](#), there were no differences in aphtas [OR 3.01 (95%CI, 0.56, 16.15)] or genital ulcers [OR 2.30 (95% CI, 0.34, 15.44)] between colchicine and placebo groups .

In [Benamour 1991](#), (autologue saliva vs placebo) there were no differences in the severity of oral aphta [OR 1.36 (95% CI, 0.38, 4.87)] or genital ulcers [OR 1.19 (95% CI, 0.21, 6.61)].

In [Davies 1988](#), there were no differences between acyclovir and placebo for the frequency of oral ulcers [WMD 3.3, (95%CI, -12.379, 18.979)] and genital ulcers [WMD 0.0 (95%CI, -9.283, 9.283)] during treatment ($p = 0.21$ according to the authors).

In [Hamuryudan 1991](#), the topical alpha-interferon was inefficacious in the prevention of new ulcers [WMD = 2.90 (95% CI: -4.396, 10.196)] and did not decrease the absolute number of ulcers in the treatment group [WMD = 1.05 (95% CI: 0.082, 2.018)].

In [Masuda 1989](#), cyclosporine resulted in significantly more alleviation of oral aphtas ulcers versus colchicine [OR 0.14, (95% CI, 0.06, 0.31)]. Clinical symptoms were significantly improved in

the cyclosporine group compared to the colchicine group [OR 0.11, (95% CI, 0.03, 0.40)].

Dermic lesions :

In [Masuda 1989](#), cyclosporine compared to colchicine alleviated dermal lesions [OR 0.30, (95% CI, 0.12, 0.75), $p < 0.01$].

Arthritis :

In [Aktulga 1980](#), (colchicine vs placebo) there was no significant difference in arthritis improvement [OR 0.49, (95% CI, 0.05, 5.11)] or arthralgia improvement [OR 0.85, (95% CI 0.06, 11.78)].

In [Calguneri 1996a](#), (colchicine vs colchicine plus benzathine-penicillin) those in the colchicine-benzathine penicillin group had significantly less arthritis episodes compared to colchicine alone [OR 0.09, (95% CI, 0.05, 0.19)]. The subgroup analysis of patients with no history of arthritis revealed a significantly higher incidence of new arthritis episodes in colchicine vs combination therapy during the follow-up period [OR 0.19, (95% CI, 0.04, 0.85), $p < 0.001$].

In the same study, a log-rank test showed a significant increase in the median duration of episode-free periods ($p < 0.001$) in the penicillin-treated patients compared with those who received colchicine alone, i.e., 13.2 months (range 5-16.4 months) versus 7.4 months (range 2-16 months). We calculated the standard deviation using the range and Chebyshev's rule, and confirmed this statistical increase in the duration of episode-free periods with a WMD of 5.80 (95% CI, 4.608, 6.992). In contrast, there were no differences between the groups in terms of duration [OR -0.50 (95% CI: -2.449, 1.449)], severity [OR 0.73 (95% CI: 0.16, 3.38)], or pattern (OR 0.94 (95% CI: 0.10, 8.71)] of the arthritis episodes that did occur.

In [Moral 1995](#), (azapropazone vs placebo), during the 3-week follow-up there were no significant differences between the two groups regarding the persistence of arthritis [OR 1.62, (95% CI, 0.58, 4.53)], the development of new attacks of arthritis [OR 0.61, (95% CI, 0.19, 1.98)] and the mean duration of arthritis [WMD 0.200, (95% CI, -4.085, 4.485)]. Joint swelling, the tender joint score and the visual analogue score improved significantly in both groups at all visits compared to the beginning of the trial, but there were no differences between groups on these parameters.

Laboratory markers:

In [Yacizi 1990](#), (azathioprine vs placebo), there was no significant difference in white cell count (WCC) between groups [OR 2.78 (95% CI: 0.82, 9.42)].

In [Moral 1995](#), (azapropazone vs placebo), there were no differences between groups at day 21 in mean C reactive protein (CRP) [WMD 1.0 (95% CI: -0.605, 2.605)] or erythrocyte sedimentation rate (ESR) [WMD 2.1 (95% CI: -11.277, 15.477)].

In [Davies 1988](#), (acyclovir vs placebo), there were no differences between groups for WCC [WMD -0.1 (95% CI: -1.105, 0.905)], immunoglobulin [WMD -0.10 (95% CI: -1.725, 1.525)], hemoglobin [WMD -0.10 (95% CI: -0.780, 0.580)] or ESR [WMD 4.60 (95% CI: -1.477, 10.677)].

DISCUSSION

The purpose of this study was to conduct a systematic review of pharmacological interventions versus either placebo or another pharmacological intervention for the treatment of the clinical features of the patients with the Behcet's syndrome.

Only studies contributing high evidence (RCTs) were reviewed. But clearly there is a lack in the performance of high methodological quality RCTs for this clinical condition. Including both double-blind trials (five) and single-blind trials (four), we include 10 studies to this review.

The allocation concealment was defined according to the definition of [Schulz 1995](#). Only two RCTs had adequate allocation concealment and eight were inadequate or unclear.

Because of the lack of common interventions and/or lack of common outcomes across trials, none of the data could be pooled. Therefore, heterogeneity was not explored and it was not possible to carry out a sensitivity analysis, dealing with differences in the effect size depending on the quality of the trials or the dosage of drugs used.

It is useful to conduct a funnel-plot to explore the existence of publication bias in a meta-analysis. To do a funnel-plot, at least 5 or 6 trials on the same outcome and intervention are required. Since only one trial was available for each outcome and intervention combination, a funnel plot was not conducted.

The studies reviewed showed methodological problems that may threaten the validity of their results. In one of these studies ([Benamour 1991](#)), 56% of the patients withdrew after randomization and before the intervention. For the final results, the intervention group comprised 30 patients and the placebo group 14. In [Calguneri 1996a](#), the study was described as single blind, but only the data analyst and main investigator were masked; the patients and physicians were not masked. In [Oryazgan 1992](#), only the ophthalmologist was masked.

In addition, several differences in the kind of interventions and described outcomes across trials were observed. Nine trials studied nine different pharmacological interventions for several different features of Behcet's syndrome. The former fact makes it impossible to pool data over either interventions or outcomes. This reflects an inconsistency in the selection and reporting of outcomes for trials evaluating therapy for Behcet's syndrome. This also demonstrates a need for more studies with either larger sample sizes or standardized outcomes so that a larger sample size is available for meta-analysis.

Because of the lack of comparability between studies, we had difficulty performing subgroup analyses. However, some authors conducted subgroup analyses that we have included. For example, [Davies 1988](#) divided the patients into those with and without previous eye involvement and [Calguneri 1996a](#), divided the patients in those with and without previous arthritis attacks.

Despite some positive results, this systematic review does not clearly support the therapeutic effect of any one of the studied interventions.

In the case of eye involvement, despite the small sample size ([BenEzra 1988](#)), visual acuity was maintained for those taking

cyclosporine compared to worsening acuity for those receiving conventional therapy (corticoids, lekeran). These results were confirmed for cyclosporine vs colchicine by [Masuda 1989](#). In contrast, despite initial eye improvement in the cyclosporine group compared to cyclophosphamide in another trial ([Oryazgan 1992](#)), the difference was not sustained after 2 years. In the trial of [Yacizi 1990](#) (azathioprine vs placebo), the patients on azathioprine with or without previous eye disease experienced significantly less eye involvement than placebo. However, the sample size was too small to generalize these results.

The trial that used benzathine-penicillin plus colchicine vs colchicine ([Calguneri 1996a](#)) showed better results in the frequency of attacks of arthritis and new episodes of arthritis for benzathine-penicillin plus colchicine. However there were no differences between both groups in terms of duration, severity or pattern of the episodes of arthritis that did occur. Azapropazone showed no benefits for arthritis involvement in Behcet's syndrome when compared to a placebo ([Moral 1995](#)).

A concern with this systematic review is the potential existence of publication bias. Thus, it is desirable that future trials use better methodology in terms of masking, reporting the flow of the participants and standardizing the outcome measures. We encourage investigators to describe fully the numbers and flow of patients by treatment groups throughout the trial and to clearly report the reasons for dropouts from each group. This review was hampered by lack of uniformity in the way these items were reported.

In summary, the results of our review do not suggest clear advantages of some classic treatments for Behcet's syndrome such as colchicine (for eye involvement, aphtas, dermal lesions or

arthritis), steroids (eye), azapropazone (arthritis) and acyclovir for aphtas. The results do suggest that cyclosporine and azathioprine are beneficial for the prevention of eye involvement, and that benzathine-penicillin helps prevent new attacks of arthritis.

AUTHORS' CONCLUSIONS

Implications for practice

Our results demonstrate the lack of efficacy of some of the classic treatments for Behcet's syndrome, including colchicine, cyclophosphamide and steroids for eye involvement, azapropazone and colchicine for arthritis and acyclovir and colchicine for aphtas.

The results confirm the protective effects of cyclosporine and azathioprine for eye involvement and benzathine-penicillin for arthritis.

Implications for research

Because of the lack of common interventions and common outcomes across trials, none of the included trials could be pooled. More randomized, placebo-controlled, double-blind trials should be carried out to compare cyclosporine, azathioprine and benzathine-penicillin vs placebo in order to make the results generalizable and comparable.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aktulga 1980

Methods	Randomized, placebo-controlled, double-blind trial.
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Aktulga 1980 (Continued)

Participants	Thirty-five patients with Behcet's disease (O'Duffy criteria). Twenty-four weeks trial Male /female ratio 3.6 Analysis exclude drop-outs (4 and 3)
Interventions	Placebo (n=17) or colchicine 0.5 mg t.i.d.
Outcomes	Assessment of aphtas Eye involvement Genital ulcers Erythema nodosum Pyoderma Arthritis Arthralgia.
Notes	Quality score=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Benamour 1991

Methods	Randomized, placebo-controlled, single-blind trial.
Participants	One hundred patients with Behcet's syndrome with either oral or genital aphtas and joint involvement were included in a 15 week trial. Exclusion criteria: patients on immunosuppressants or on corticoids. There were no differences pre-trial except for the presence of joint lesion (intervention 73%, placebo 57%). Fifty-six withdrawals before intervention.
Interventions	Five intradermal injections per week (after 5th week two injections per week) of progressively diluted (from 1/10 000 000 to 1/100 in a period of 5 weeks) autologous saliva (n=30) or physiological serum (n=14).
Outcomes	Rate of improvement of oral and genital aphtas Joint involvement.
Notes	Quality score=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Benezra 1988

Methods	Randomized, controlled, single-blind trial.
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Pharmacotherapy for Behcet's syndrome (Review)

Benezra 1988 (Continued)

Participants	Forty patients with ocular Behcet's syndrome were included in a 104 weeks trial. No clear statement of inclusion/exclusion criteria.
Interventions	Cyclosporin A 10 mg/kg/d was tapered to 5 mg/kg/d (n=20) or conventional therapy: (n=20) 1 to 1.5 mg prednisolone/kg/d or chlorambucil 0.1-0.2 mg/kg/d and the dosage was lowered according to clinical response.
Outcomes	Visual acuity, mouth ulcers, genital ulcers. Patients drop-outs because severity of eye involvement.
Notes	Quality score=2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Calguneri 1996a

Methods	Randomized, controlled, single-blind (data analyst and the independent investigator) clinical trial.
Participants	Hundred and twenty patients (1.07 male/female ratio) were included in a 104 week trial. Inclusion criteria: Int. Study Group. No significant differences between groups pre-trial. Mean age 36.8 sd 9.6 Intention to treat analysis.
Interventions	Colchicine 1.5 mg/day (n=60) or colchicine plus intramuscular benzathine-penicilline 1.2 million ui/3 weeks (n=60).
Outcomes	Arthritis: incidence, duration, severity and pattern of attacks. Co-interventions: corticoids. Duration of arthritis episode-free periods. Subgroup analysis: patients with no prior history of arthritis.
Notes	Quality score=2 Neither dropouts nor withdrawals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Davies 1988

Methods	Randomized, placebo-controlled, double-blind, clinical trial. Crossover design.
Participants	Twenty-two patients with recurrent oral and genital ulceration (Mason and Barnes criteria for Behcet's syndrome) were included in a 24 week trial. Patients with life-threatening or severe complications such as active uveitis were excluded. Mean age 43 (range 18-55 years). Males/women 7/15.

Davies 1988 (Continued)

Drop-outs: two patients on active treatment, one because unacceptably active disease. Four withdrawals.

Interventions	Acyclovir (n=22) (4000 mg/day/1 week, followed by 800 mg daily for 11 weeks) or placebo (n= 22). Four weeks of washout and they crossed to the missed intervention for an additional period of 12 weeks. Six patients were on corticoids, one on azathioprine, and a second aspirin, during the whole trial.
Outcomes	Frequency of oral ulcers, new lesions. Frequency of genital ulcers, new lesions. ESR, Hb, WBC, IgG.
Notes	Quality score=5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hamuryudan 1991

Methods	Randomized, placebo-controlled, double-blind trial.
Participants	Sixty-three behcet's patients (26 males, 37 females) with active oral ulcers were included in a 24-week trial. Two withdrawals (1/1).
Interventions	Topical Interferon-alpha-2c hydrogel (1×10^5 U/g) qid (n=30) vs placebo (n=31).
Outcomes	New ulcers, total ulcers.
Notes	Quality score=3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Masuda 1989

Methods	Randomized, controlled, double-blind trial.
Participants	Ninety-six patients aged 15 years or more with Behcet's syndrome, whose visual acuity was 20/40 or less, and who experienced at least two episodes of ocular attack during the prior 16 weeks, were included in a 16 weeks trial. There were no significant differences between the two groups pre-trial. Dropouts: renal dysfunction in 1 cyclosporin case and hepatic dysfunction in two colchicine cases.
Interventions	Cyclosporin 10 mg/kg/day (n=47) or colchicine 1 mg/day (n=46).
Outcomes	Frequency of ocular attack Visual acuity Ocular manifestations

Pharmacotherapy for Behcet's syndrome (Review)

Masuda 1989 (Continued)

Systemic symptoms.

Notes	Quality score=3	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Moral 1995

Methods	Randomized, placebo-controlled, double-blind clinical trial.	
Participants	Sixty-three Behcet's patients with acute arthritis of up to 10 days of duration were included in a 3 weeks trial. Twenty-eight patients (14 males, 14 females; mean age 36.2 sd 8.1 years) from azapropazone, and 29 patients (18 males, 11 females; mean age 34.2 sd 8.4 years) from the placebo completed the trial. Exclusion: patients on NSAID and those with contraindication to NSAID. No dropouts.	
Interventions	Azapropazone 300 mg or placebo qid. Use of acetaminophen was allowed and the number of tablets recorded. Six patients were on azathioprine (3 / 3), and 11 (6 AZP / 5 PBO) were on colchicine, during the trial.	
Outcomes	Persistence of Arthritis New Arthritis Mean episode duration Joint swelling Tender joint score Visual analogue scale for pain Mean CRP mg/dl Mean ESR, mm/hour.	
Notes	Quality score=3	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Oryazgan 1992

Methods	Randomized, controlled, single-mask (the ophthalmological examination) clinical trial.	
Participants	Twenty-three patients with Behcet's syndrome and bilateral, severe, reversible uveitis with posterior involvement and at least three ocular disease attacks within the previous 6 months were included in a 104 week trial, of them a mean of 52 weeks masked. Exclusion: end stage disease, irreversible retinal damage, blindness, on immunosuppressive agents. No pre-treatment differences between groups except for sex. Women did not accept to be included in Cyc A group because risk of hirsutism. Mean age 29 sd 6 (Cyc A), mean 32 sd 6 (CTX). Mean visual acuity at entry 4.46 sd 2.96 (Cyc A) 4.77 2.65 (CTX).	

Pharmacotherapy for Behcet's syndrome (Review)

Oryazgan 1992 (Continued)

Duration of eye disease in years 2.64 sd 1.58 (Cyc A), 2.39 sd 2.37 (CTX).
No dropouts.

Interventions	Oral cyclosporin A 5 mg/kg/day (n=12) or monthly intravenous 1 g boluses of cyclophosphamide (n=11). Three patients were on corticoids during the trial (1/2).
Outcomes	Improvement of visual acuity Incidence of ocular attacks/patient/month
Notes	Quality score=0

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Yacizi 1990

Methods	Randomized, placebo-controlled, double-blind clinical trial.
Participants	O'Duffy's criteria for diagnosis of Behcet's syndrome Exclusion: irreversible bilateral eye disease, fundi not assessable, those on immunosuppressive agents, levamisole or penicillamine in the previous 3 months or corticoids in the last month. Group I: under 40 years, whose duration of disease was 24 months or less, without evidence of uveitis (n=25), and group II: patients of any age and any duration of the disease with eye disease (n=48), were included in a 104 week trial. Dropouts: 6 in the group 2 on placebo, because of severe eye disease. Intention to treat analysis.
Interventions	Group I: azathioprine 2.5 mg/kg (n=12) or placebo (n=13) and group II: azathioprine 2.5 mg/kg (n=25) or placebo (n=23). Corticosteroid treatment remained available to all patients.
Outcomes	Azathioprine effect on preexisting eye disease and prevention of new eye disease Withdrawals due to eye disease Development of new eye disease Involvement of previously unaffected eye Hypopyon uveitis Corticosteroid treatment of deteriorating eye disease Change in visual acuity Side effects.
Notes	Quality score=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdalla 1973	Open.
Bach 1997	Editorial.
Chavis 1992	Open.
Elidan 1991	Uncontrolled.
Gardner-Medwin 1994	Retrospective.
Hamuryudan 1990	Open.
Hamuryudan 1994	Open.
Hamuryudan 1997	Follow-up of Yacizi 1990.
Ince 1996	To assess toxicity of methotrexate in rheumatoid arthritis patients, a questionnaire was used. To test its credibility it was tested in four different groups of patients. One of them was a Behcet's patient.
Kazokoglu 1991	Open.
Mochizuki 1991	Open.
Nussenblatt 1983a	Uncontrolled
Nussenblatt 1983b	Uncontrolled.
Nussenblatt 1985a	Follow-up.
Nussenblatt 1985b	Follow-up.
Nussenblatt 1996	Pilot study. Not controlled. Two patients.
Nussenblatt 1997	Forty patients with uveitis were included in the trial, but only seven with Behcet's syndrome. No characteristics, withdrawals or outcomes are isolated and available for the Behcet's syndrome patients.
Sakane 1995	Open.
Simsek 1991	Open.
Wechsler 1988	Review.
Whitcup 1994	Retrospective.

DATA AND ANALYSES

Comparison 1. Azathioprine vs Placebo. No previous eye involvement.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Necessitating withdrawal	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 New eye disease	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.02, 0.54]
3 Hypopyon uveitis	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Pulsed intravenous corticosteroid treatment	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.00, 7.39]
5 Oral corticosteroid treatment	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Azathioprine vs Placebo. No previous eye involvement., Outcome 1 Necessitating withdrawal.

Study or subgroup	Azathioprine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Yacizi 1990	0/12	0/13			Not estimable
Total (95% CI)	12	13			Not estimable
Total events: 0 (Azathioprine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Analysis 1.2. Comparison 1 Azathioprine vs Placebo. No previous eye involvement., Outcome 2 New eye disease.

Study or subgroup	Azathioprine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Yacizi 1990	1/12	8/13		100%	0.11[0.02,0.54]
Total (95% CI)	12	13		100%	0.11[0.02,0.54]
Total events: 1 (Azathioprine), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.71(P=0.01)

Analysis 1.3. Comparison 1 Azathioprine vs Placebo. No previous eye involvement., Outcome 3 Hypopyon uveitis.

Study or subgroup	Azathioprine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Yacizi 1990	0/12	0/13			Not estimable

Analysis 1.4. Comparison 1 Azathioprine vs Placebo. No previous eye involvement., Outcome 4 Pulsed intravenous corticosteroid treatment.

Analysis 1.5. Comparison 1 Azathioprine vs Placebo. No previous eye involvement., Outcome 5 Oral corticosteroid treatment.

Comparison 2. Azathioprine vs Placebo. Previous eye involvement.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Necessitating withdrawal.	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.02, 0.53]
2 New eye disease.	1	14	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.06 [0.01, 0.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Involvement of previously unaffected eye.	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.02, 0.64]
4 Hypopyon uveitis	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.03, 0.70]
5 Pulsed intravenous corticosteroid treatment.	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.13, 1.39]
6 Oral Corticosteroid treatment.	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.04, 1.54]

Analysis 2.1. Comparison 2 Azathioprine vs Placebo. Previous eye involvement., Outcome 1 Necessitating withdrawal..

Analysis 2.2. Comparison 2 Azathioprine vs Placebo. Previous eye involvement., Outcome 2 New eye disease..

Analysis 2.3. Comparison 2 Azathioprine vs Placebo. Previous eye involvement., Outcome 3 Involvement of previously unaffected eye..

Analysis 2.4. Comparison 2 Azathioprine vs Placebo. Previous eye involvement., Outcome 4 Hypopyon uveitis.

Analysis 2.5. Comparison 2 Azathioprine vs Placebo. Previous eye involvement., Outcome 5 Pulsed intravenous corticosteroid treatment..

Analysis 2.6. Comparison 2 Azathioprine vs Placebo. Previous eye involvement., Outcome 6 Oral Corticosteroid treatment..

Comparison 3. Azathioprine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity [first minus last visit] mean sd	1	63	Mean Difference (IV, Fixed, 95% CI)	-0.91 [-1.96, 0.14]
2 GI side effects	1	1394	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [1.06, 1.79]
3 Low WCC (<4,000/ml)	1	57	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.78 [0.82, 9.42]
4 IV steroids neccessity	1	73	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.10, 0.69]

Analysis 3.1. Comparison 3 Azathioprine vs placebo, Outcome 1 Visual acuity [first minus last visit] mean sd.

Study or subgroup	Azathioprine		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI			
	N	Mean(SD)	N	Mean(SD)						
Yacizi 1990	34	0.2 (1.4)	29	1.1 (2.6)		100%	-0.91[-1.96,0.14]			
Total ***	34		29			100%	-0.91[-1.96,0.14]			
Heterogeneity: Not applicable										
Test for overall effect: Z=1.7(P=0.09)										
Favours Azathioprine					-10	-5	0	5	10	Favours Placebo

Analysis 3.2. Comparison 3 Azathioprine vs placebo, Outcome 2 GI side effects.

Study or subgroup	Azathioprine	Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Yacizi 1990	174/782	105/612		100%	1.37[1.06,1.79]
Total (95% CI)	782	612		100%	1.37[1.06,1.79]
Total events: 174 (Azathioprine), 105 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.36(P=0.02)					
<div><div>Favours Azathioprine</div><div>0.10.20.512510</div><div>Favours Placebo</div></div>					

Analysis 3.3. Comparison 3 Azathioprine vs placebo, Outcome 3 Low WCC (<4,000/ml).

Study or subgroup	Azathioprine	Placebo	Peto Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI			Peto, Fixed, 95% CI
Yacizi 1990	11/34	3/23			100%	2.78[0.82,9.42]
			Favours Azathioprine	0.1 0.2 0.5 1 2 5 10	Favours Placebo

Analysis 3.4. Comparison 3 Azathioprine vs placebo, Outcome 4 IV steroids necessity.

Comparison 4. Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of arthritis episodes	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.09 [0.05, 0.19]
2 Patients with arthritis episodes	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Arthritis episodes in patients without prior history of arthritis	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.04, 0.85]
2.2 Number of patients with arthritis episodes	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.10, 0.47]
3 Mean of arthritis episodes per patient	1	120	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-0.81, -0.39]
4 Duration of episode	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.45, 1.45]
5 Severe arthritis attacks	1	62	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.16, 3.38]
6 Polyarticular joint involvement	1	62	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.10, 8.71]
7 Prednisone dosage/day	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.31, 0.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Prednisone duration/days	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.42, 1.02]
9 Duration of arthritis episode-free period	1	120	Mean Difference (IV, Fixed, 95% CI)	5.80 [4.61, 6.99]
10 Colchicine gastro-intestinal side effects.	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.38, 3.73]

Analysis 4.1. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 1 Incidence of arthritis episodes.

Analysis 4.2. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 2 Patients with arthritis episodes.

Analysis 4.3. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 3 Mean of arthritis episodes per patient.

Analysis 4.4. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 4 Duration of episode.

Analysis 4.5. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 5 Severe arthritis attacks.

Analysis 4.6. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 6 Polyarticular joint involvement.

Analysis 4.7. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 7 Prednisone dosage/day.

Analysis 4.8. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 8 Prednisone duration/days.

Analysis 4.9. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 9 Duration of arthritis episode-free period.

Analysis 4.10. Comparison 4 Colchicine plus Benzathine Penicillin vs Colchicine. Arthritis, Outcome 10 Colchicine gastro-intestinal side effects..

Comparison 5. Topical alpha interferon vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New oral ulcers (per group)	1	61	Mean Difference (IV, Fixed, 95% CI)	2.90 [-4.40, 10.20]
2 Total oral ulcers (per patient)	1	61	Mean Difference (IV, Fixed, 95% CI)	1.05 [0.08, 2.02]

Analysis 5.1. Comparison 5 Topical alpha interferon vs placebo, Outcome 1 New oral ulcers (per group).

Analysis 5.2. Comparison 5 Topical alpha interferon vs placebo, Outcome 2 Total oral ulcers (per patient).

Comparison 6. Azapropazone vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistence of arthritis	1	57	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.58, 4.53]
2 New arthritis	1	57	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.19, 1.98]
3 Duration of arthritis (mean±sd days)	1	57	Mean Difference (IV, Fixed, 95% CI)	0.20 [-4.08, 4.48]
4 Joint swelling day 7	1	57	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.52, 0.52]
5 Joint swelling day 21	1	57	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.42, 0.62]
6 Tender joint score 7	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.62, 0.22]
7 Tender joint score 21	1	57	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.34, 0.54]
8 Visual analogue scale for pain day 7	1	57	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.19, -0.21]
9 Visual analogue score for pain day 21	1	57	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.14, 2.14]
10 Mean C reactive protein (mg/dl) day 21	1	57	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.61, 2.61]
11 Mean erythrocyte sedimentation rate day 21	1	57	Mean Difference (IV, Fixed, 95% CI)	2.10 [-11.28, 15.48]

Analysis 6.1. Comparison 6 Azapropazone vs placebo, Outcome 1 Persistence of arthritis.

Analysis 6.2. Comparison 6 Azapropazone vs placebo, Outcome 2 New arthritis.

Analysis 6.3. Comparison 6 Azapropazone vs placebo, Outcome 3 Duration of arthritis (mean±sd days).

Analysis 6.4. Comparison 6 Azapropazone vs placebo, Outcome 4 Joint swelling day 7.

Analysis 6.5. Comparison 6 Azapropazone vs placebo, Outcome 5 Joint swelling day 21.

Analysis 6.6. Comparison 6 Azapropazone vs placebo, Outcome 6 Tender joint score 7.

Analysis 6.7. Comparison 6 Azapropazone vs placebo, Outcome 7 Tender joint score 21.

Analysis 6.8. Comparison 6 Azapropazone vs placebo, Outcome 8 Visual analogue scale for pain day 7.

Analysis 6.9. Comparison 6 Azapropazone vs placebo, Outcome 9 Visual analogue score for pain day 21.

Analysis 6.10. Comparison 6 Azapropazone vs placebo, Outcome 10 Mean C reactive protein (mg/dl) day 21.

Analysis 6.11. Comparison 6 Azapropazone vs placebo, Outcome 11 Mean erythrocyte sedimentation rate day 21.

Comparison 7. Cyclosporine vs cyclophosphamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity	1	20	Mean Difference (IV, Fixed, 95% CI)	0.80 [-2.52, 4.12]
2 Number of ocular attacks/patient/month up to 6 months.	1	22	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.35, 0.07]
3 Number of ocular attacks/patient/month from 6 months to unmasking.	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.56, 0.34]

Analysis 7.1. Comparison 7 Cyclosporine vs cyclophosphamide, Outcome 1 Visual acuity.

**Analysis 7.2. Comparison 7 Cyclosporine vs cyclophosphamide,
Outcome 2 Number of ocular attacks/patient/month up to 6 months..** **Analysis 7.3. Comparison 7 Cyclosporine vs cyclophosphamide, Outcome
3 Number of ocular attacks/patient/month from 6 months to unmasking..** **Comparison 8. Autologous saline vs placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral aphtas improvement	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.38, 4.87]
2 Genital aphtas improvement	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.21, 6.61]
3 Arthritis improvement	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Autologous saline vs placebo, Outcome 1 Oral aphtas improvement.

Analysis 8.2. Comparison 8 Autologous saline vs placebo, Outcome 2 Genital aphtas improvement.

Analysis 8.3. Comparison 8 Autologous saline vs placebo, Outcome 3 Arthritis improvement.

Comparison 9. Cyclosporine vs conventional therapy.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Drop-outs due to severe eye involvement	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.05, 0.84]
2 Visual acuity at 1st month	1	54	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.12, 0.26]
3 Visual acuity at 24 month	1	24	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.16, 0.40]
4 Mouth ulcers: 0-24 months	1	6	Peto Odds Ratio (Peto, Fixed, 95% CI)	20.09 [0.31, 1283.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Genital ulcers:0-24 months	1	6	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Cyclosporine vs conventional therapy., Outcome 1 Drop-outs due to severe eye involvement.

Analysis 9.2. Comparison 9 Cyclosporine vs conventional therapy., Outcome 2 Visual acuity at 1st month.

Analysis 9.3. Comparison 9 Cyclosporine vs conventional therapy., Outcome 3 Visual acuity at 24 month.

Analysis 9.4. Comparison 9 Cyclosporine vs conventional therapy., Outcome 4 Mouth ulcers: 0-24 months.

Analysis 9.5. Comparison 9 Cyclosporine vs conventional therapy., Outcome 5 Genital ulcers:0-24 months.

Comparison 10. Colchicine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Aphthas not improved	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [0.56, 16.15]
2 Eye not improved	1	15	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.06, 3.78]
3 Genital ulcers not improved	1	17	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.30 [0.34, 15.43]
4 Erythema nodosum not improved	1	9	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.04, 7.61]
5 Pyoderma not improved	1	26	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.31, 6.97]
6 Arthritis not improved	1	10	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.05, 5.11]
7 Arthralgia not improved	1	11	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.06, 11.78]
8 Bilateral eye involvement	1	35	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.06, 17.70]

Analysis 10.1. Comparison 10 Colchicine vs placebo, Outcome 1 Aphtas not improved.

Analysis 10.2. Comparison 10 Colchicine vs placebo, Outcome 2 Eye not improved.

Analysis 10.3. Comparison 10 Colchicine vs placebo, Outcome 3 Genital ulcers not improved.

Analysis 10.4. Comparison 10 Colchicine vs placebo, Outcome 4 Erythema nodosum not improved.

Analysis 10.5. Comparison 10 Colchicine vs placebo, Outcome 5 Pyoderma not improved.

Analysis 10.6. Comparison 10 Colchicine vs placebo, Outcome 6 Arthritis not improved.

Analysis 10.7. Comparison 10 Colchicine vs placebo, Outcome 7 Arthralgia not improved.

Analysis 10.8. Comparison 10 Colchicine vs placebo, Outcome 8 Bilateral eye involvement.

Comparison 11. Cyclosporine vs Colchicine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ocular attacks frequency: not improved	1	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.04, 0.23]
2 Ocular attacks severity: not improved	1	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.04, 0.23]
3 Dermal lesions not improved	1	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.12, 0.75]
4 Aphas not improved	1	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.06, 0.31]
5 Clinical symptoms aggravated	1	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.03, 0.40]

Analysis 11.1. Comparison 11 Cyclosporine vs Colchicine, Outcome 1 Ocular attacks frequency: not improved.

Analysis 11.2. Comparison 11 Cyclosporine vs Colchicine, Outcome 2 Ocular attacks severity: not improved.

Analysis 11.3. Comparison 11 Cyclosporine vs Colchicine, Outcome 3 Dermal lesions not improved.

Analysis 11.4. Comparison 11 Cyclosporine vs Colchicine, Outcome 4 Aftas not improved.

Analysis 11.5. Comparison 11 Cyclosporine vs Colchicine, Outcome 5 Clinical symptoms aggravated.

Comparison 12. Acyclovir vs placebo.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency new oral ulcers.	1	44	Mean Difference (IV, Fixed, 95% CI)	3.30 [-12.38, 18.98]
2 Frequency new genital ulcers.	1	44	Mean Difference (IV, Fixed, 95% CI)	0.0 [-9.28, 9.28]
3 Erythrocyte sedimentation rate mm/h.	1	44	Mean Difference (IV, Fixed, 95% CI)	4.60 [-1.48, 10.68]
4 Hemoglobine g/dl.	1	44	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.78, 0.58]
5 White cell count, 10 ⁹ /l.	1	44	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.10, 0.90]
6 Inmunoglobulin G, g/l.	1	44	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.73, 1.53]

Analysis 12.1. Comparison 12 Acyclovir vs placebo., Outcome 1 Frequency new oral ulcers..

Analysis 12.2. Comparison 12 Acyclovir vs placebo., Outcome 2 Frequency new genital ulcers..

Analysis 12.3. Comparison 12 Acyclovir vs placebo., Outcome 3 Erythrocyte sedimentation rate mm/h..

Analysis 12.4. Comparison 12 Acyclovir vs placebo., Outcome 4 Hemoglobine g/dl..

Analysis 12.5. Comparison 12 Acyclovir vs placebo., Outcome 5 White cell count, $10^9/l.$

Analysis 12.6. Comparison 12 Acyclovir vs placebo., Outcome 6 Immunoglobulin G, g/l..

APPENDICES

Appendix 1. Full search strategy

001 behcet's syndrome/ 3007
002 triple symptom complex.tw. 6
003 behcet\$.tw. 2831
004 or/1-3 3281
005 clinical trial.pt. 205256
006 randomized controlled trial.pt. 89327
007 random allocation/ 36248
008 exp clinical trials/ 97627
009 exp longitudinal studies/ 275490
010 double-blind method/ 49155
011 single-blind method/ 3268
012 placebos/ 17977
013 random\$.tw. 143168
014 placebo\$.tw. 49182
015 (control or controls or controlled).tw. 717939
016 (double adj blind\$).tw. 44078
017 or/5-16 1167549
018 4 and 17 480

WHAT'S NEW

Date	Event	Description
8 November 2008	Amended	Converted to new review format. CMSG ID: C065-R

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- CCOHTA. Canadian Coordinating Office for Health Technology Assessment .Ottawa, Canada.
- Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Madrid, Spain.
- INSALUD. Madrid, Spain.
- Clinical Epidemiology Unit, University of Ottawa. Ottawa, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acyclovir [therapeutic use]; Anti-Infective Agents [therapeutic use]; Apazone [therapeutic use]; Azathioprine [therapeutic use]; Behcet Syndrome [*drug therapy]; Colchicine [therapeutic use]; Cyclosporine [therapeutic use]; Immunosuppressive Agents [therapeutic use]; Interferon-alpha [therapeutic use]; Penicillins [therapeutic use]

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