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[Intervention Review]

Cyclosporine for treating rheumatoid arthritis

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ABSTRACT

Background

Rheumatoid arthritis (RA) is an autoimmune disease characterized by an activation of T lymphocyte and an increase in interleukine turnover. In RA, cyclosporine is known to be efficient as a Disease Modifying Anti-Rheumatic Agent (DMARD), especially when other treatments such as injectable gold, D-penicillamine or anti-malarials were not efficacious.

Objectives

To estimate the short-term (up to one year) effects of cyclosporine for rheumatoid arthritis.

Search methods

We searched the Cochrane Musculoskeletal Group trials register, and MEDLINE, up to 1997, using the search strategy developed by the Cochrane Collaboration (Dickersin 1994). The search was complemented with bibliography searching of the reference list of the trials retrieved from the electronic search. Key experts in the area were contacted for further published and unpublished articles.

Selection criteria

All randomized clinical trials (RCTs) and controlled clinical trials (CCTs) comparing cyclosporine against placebo in patients with rheumatoid arthritis.

Data collection and analysis

Two reviewers determined the trials to be included based on inclusion and exclusion criteria (GW, MSA). Data were independently abstracted by two reviewers (DH, GW),and checked by a third reviewer (BS) using a pre-developed form for the rheumatoid arthritis sub-group of the Cochrane Musculoskeletal Group.

Methodological quality of the RCTs and CCTs was assessed by two reviewers (BS, DH). Rheumatoid arthritis outcome measures were extracted from the publications for change from baseline endpoints. Sufficient data were obtained to include in the pooled analysis the number of swollen joints, physician global assessment, patient global assessment and erythrocyte sedimentation rate (ESR).

Main results

Three trials and 318 patients were included. A statistically significant decrease in the number of tender and swollen joints was observed for cyclosporine when compared to placebo. The standardized mean difference (SMD) for the change in the number of swollen joints was -0.969. Significant improvements in pain and the functional index were also found for cyclosporine. More side effects occurred in the cyclosporine group compared to placebo.

Authors' conclusions

Cyclosporine has an important clinical benefit in the short-term (up to one year) treatment of patients with progressive rheumatoid arthritis.

PLAIN LANGUAGE SUMMARY

Cyclosporine for treating rheumatoid arthritis

This review included three trials with a total of 318 patients. A statistically significant decrease in the number of tender and swollen joints was found for patients taking cyclosporine when compared to those taking placebo. Significant improvements in pain and function were also found for those patients taking cyclosporine. More side effects occurred in the cyclosporine group compared to the placebo group.

Cyclosporine has an important clinical benefit in the short-term (up to one year) treatment of patients with progressive rheumatoid arthritis.

BACKGROUND

Rheumatoid arthritis (RA) is an autoimmune disease characterized by an activation of T lymphocyte and an increase in interleukine turnover (Waalen 1987). Cyclosporine is a fungal peptide with immunosuppressive properties, inhibiting T lymphocytes and the production of cytokines (Hess 1982) and has been used as an antimetic agent to prevent graft rejection. As for RA, cyclosporine is known to be efficient as a Disease Modifying Anti-Rheumatic Agent (DMARD), especially when other treatments such as injectable gold, D-penicillamine or anti-malarials were not efficacious.

The first trials used cyclosporine with high doses and doses had to be decreased because of adverse effects, such as hypertension or increasing creatinemiea. Subsequent study designs started with low doses, and doses were increased when no adverse effects were seen with respect to blood counts or renal function. Preliminary open uncontrolled studies have been constructed using high doses of cyclosporine (10mg/kg/day) (Dougados 1993). It was clear that the effect of cyclosporine and the side effects were modulated by the doses of the drug. A few placebo controlled studies used initial low doses of the drug (2.5-5 mg/kg/day) to minimize the side effects (Tugwell 1990, Dougados 1988, Forre 1994). The average dose of cyclosporine ranges from 3.7 to 4.4 mg/kg/day.

The estimate of the magnitude of the clinical benefits and side effects found with cyclosporine in RA varies considerably across studies. Data obtained with these studies suggest that cyclosporine is more than a symptomatic treatment of RA but can be also considered as a DMARD, in terms of the effect of this drug on the evolution of the disease (Dougados 1993). Data of previous studies agree that cyclosporine is effective and probably of benefit in patients with active diseases and refractory RA (Intl consensus 1993).

Further trials have studied the efficacy of cyclosporine versus other DMARDs, including azathioprine (Kruger 1992) and D-penicillamine (Van Rijthoven 1991) or the efficacy of cyclosporine combined with other treatment, such as vitamin D (Gepner 1989) and Bromocriptine (Dougados 1988).

OBJECTIVES

To conduct a systematic review of the literature on the short term efficacy and toxicity of cyclosporine.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized clinical trials (RCTs) and controlled clinical trials (CCTs) published in English, with a minimum duration of study of 16 weeks.

Types of participants

Patients with a diagnosis of rheumatoid arthritis according to the American Rheumatism Association (ARA) criteria for classic or definite RA (specific details of the activity of RA stated in the publications).

Types of interventions

Intervention group : cyclosporine for at least 16 weeks.
Control group : placebo.

Types of outcome measures

All the outcome measures in OMERACT (OMERACT 1993) were included for the planned analysis, although only some were consistently measured.

OMERACT measures for efficacy include :
a) Number of tender joints
b) Number of swollen joints
c) Acute phase reactants
d) Pain
e) Functional status
f) Physician global assessment
g) Patient global assessment
h) Radiological damage

Toxicity was evaluated using withdrawals and dropouts (total and organ-specific).

Search methods for identification of studies

An electronic literature search was conducted using MEDLINE, from 1966 to 1997, using the search strategy developed by the Cochrane Collaboration (Dickersin 1994). The search was complemented with bibliography searching of the reference list of the trials retrieved from the electronic search. Key experts in the area were contacted for further published and unpublished articles.

Data collection and analysis

Data extracted from the publications included study characteristics and outcome measures of efficacy and toxicity. The toxicity results were generally reported as overall results at the end of the trial, and were therefore pooled for different trial follow-ups. Toxicity was analyzed using a pooled odds ratio for total withdrawals, and dropouts and withdrawals for specific reasons.

Heterogeneity was estimated using a chi-square test. Fixed effects models were carried out throughout, except when heterogeneity existed, in which case, a random effects model was used.

RESULTS

Description of studies

Three RCTs met the criteria for inclusion (Tugwell 1990, Dougados 1988, Forre 1994). One study was excluded (Van Rijthoven 1986) because of the high dose of cyclosporine (10 mg/kg/day) used. Tugwell did not use the Ritchie index but the number of joints (0 to 68 for tender and 0 to 66 for swollen joints). Forre used a pain score from 0 to 4 whereas Tugwell and Dougados used a 10 cm visual analogue scale (VAS) for pain. Duration of morning stiffness was measured in hours by Tugwell and in minutes in the other studies. The Lee functional index was not used by Tugwell. Different scales were used to assess patient or physician overall assessment. These assessments were transformed to a 7 point scale from -3 to 3.

Risk of bias in included studies

The methodological quality of the studies was assessed independently by 2 of the reviewers (BS, DH) using a validated

and published quality scale (Jadad 1996). This scale includes an assessment of randomization, double-blinding procedures and description of withdrawals. The possible range of scores is 0 (worst) to 5 (best). Two of the studies had a score of 4 and the other a score of 5. The kappa for agreement between observers on the quality scores was 1.0.

Effects of interventions

There was a statistically significant reduction in the number of tender (SMD=-0.60, 95% CI: -0.934, -0.266) and swollen (SMD=-0.623, 95% CI: -0.851, -0.395) joints using cyclosporine compared to placebo. Statistically significant differences favouring cyclosporine were also observed for pain, Lee's functional index and Ritchie joint score.

The data available on side effects indicated more side effects with cyclosporine, namely: headache (OR=3.4, 95% CI: 1.1, 10.4), tremor (OR=5.3, 95% CI: 2.8, 9.9), dyspepsis (OR=2.0, 95% CI: 1.1, 3.6), nausea (OR=2.2, 95% CI: 1.2, 3.8), paraesthesia (OR = 2.3, 95% CI: 1.1, 4.9) and gum hyperplasia (OR = 8.0, 95% CI: 2.1, 30.2).

DISCUSSION

Heterogeneity was not an important factor in the evaluation of the RCTs and the results are presented are based on a fixed effects approach. The purpose of this systematic review was to evaluate the efficacy and toxicity of cyclosporine treatment of patients with RA. The studies pooled all directly addressed the objective and used similar criteria for RA, the disease of interest. Study selection bias was minimized by selecting only randomized trials. Although some of the major outcome measures in the trials were sufficiently homogeneous to allow pooling, there was some lack of standardization of the outcome measurements and even omission of some in some studies. These studies were all conducted before the establishment of the OMERACT and the American College of Rheumatology (ACR) core set of measures for RA. Many of the measures evaluated are considered nowadays of doubtful value (eg. grip strength). There was some degree of consistency in the reporting of results, with the endpoints presented as simple change from baseline.

The pooled estimate of clinical benefit from cyclosporine in the present meta-analysis provides an estimate of benefit that makes appropriate adjustments for the different sample sizes and degree of precision across the studies. It also takes into account the use of different scoring techniques by standardizing the weighted differences (e.g. different number of possible swollen joints measured in each study). The variables for which there was sufficient data for pooling (number of swollen joints, VAS Pain and Lee's functional index) all showed a statistically significant benefit when compared to placebo.

Toxicity was increased in the cyclosporine group. The following side effects were 2 to 5 fold more likely to occur with cyclosporine then placebo: headaches, tremor, dyspepsis, nausea and paresthesia. Cohort studies may be more appropriate to evaluate the incidence of these disorders.

Cyclosporine has an important clinical benefit in the short term for patients with progressive rheumatic disease.

AUTHORS' CONCLUSIONS

Implications for practice

Positive effects using cyclosporine were obtained in trials involving patients with very severe refractory active RA. Clinically, restriction of the drug to such individuals is suggested by its potentially irreversible toxicity.

Implications for research

Since there are additional specific issues particularly relevant to slow acting antirheumatic drugs, it might be useful to consider establishing supplementary guidelines or criteria for the standardization of reporting for clinical trials of antirheumatic drugs, following the guidelines from CONSORT (Bedd 1996); this would avoid the need to obtain additional data and analyses from the original investigators (which is often hard to obtain after the study is published). Specific issues for RA include:

(1) Standardization of timing: there is considerable variation in the duration of trials of many of the slow acting anti-rheumatic drugs which makes it difficult to compare them; thus the timing of assessments should be at regular intervals, preferably standardized, so that studies of longer duration can be compared with shorter ones using data at the same points in time. The clinical heterogeneity in the follow-up duration of the studies included in this review only allowed us to pool results for the first 6 months of treatment.
(2) Comparability of groups: the description of the demographic and clinical characteristics of the patients is important, to allow for meaningful pooling of results and generalizability
(3) Details of the inclusion and exclusion criteria are also needed for deciding on the generalizability of the results. For example, there are frequently age restrictions because of the regulatory agencies' concerns about toxicity in the elderly, yet this age group poses major therapeutic challenges and good quality data are needed for informed decisions.
(4) Different drug studies use different outcomes and different methods of measuring them, making it difficult or impossible to compare or combine the results. These issues will hopefully be resolved by applying the criteria established by OMERACT and the ACR in relation to the evaluation of patients with RA in clinical trials.
(5) Some studies publish only the end-of-treatment results while others publish the difference between beginning and end of treatment; some publish their statistics as medians while others publish just means. For valid meta-analysis (or simple comparisons by clinicians reading the articles) manuscripts should provide standardized data on each endpoint, perhaps a minimum of the following: means and medians of each one at baseline and at end of treatment, plus their variance.
(6) Although the reporting of means or medians is the traditional method of reporting the magnitude of benefit, clinical significance can be usefully complemented by reporting the proportion of patients achieving a predetermined degree of improvement. This provides useful information to the clinician on the probability of a major improvement. Several sets of criteria are available (Paulus, ACR and Eular). This information on the proportion of patients achieving a specified level of improvement can be combined across studies. The proportion of patients improving or developing adverse reactions, rather than means, is also needed for developing decision analysis algorithms, another important application of a pooled estimate.

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REFERENCES

References to studies included in this review

Dougados 1988 *{published data only}*

Dougados M, Awada H, Amor B. Cyclosporin in rheumatoid arthritis : a double blind, placebo controlled study in 52 patients. *Ann Rheum Dis* 1998;**47**:127-33.

Forre 1994 *{published data only}*

Forre O and the Norvegian Arthritis Study Group. Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine. *Arthritis Rheum* 1994;**37**:1506-12.

Tugwell 1990 *{published data only}*

Tugwell P, Bombardier C, Gent M, et al. Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. *Lancet* 1990;**335**:1051-5.

References to studies excluded from this review

Van Rijthoven 1986 *{published data only}*

Van Rijthoven A, Dijkmans BA, Goei The H, et al. Cyclosporin treatment for rheumathoid arthritis : a placebo controlled, double-blind, multicenter study. *Ann Rheum Dis* 1986;**45**:726-31.

Additional references

Dickersin 1994

Dickersin K. , Scherer R., Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286-91.

Dougados 1988

Dougados M, Duchene l, Amor B. Bromocriptin and cyclosporine A combination therapy in rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:1331-4.

Dougados 1993

Dougados M, Torley H. Efficacy of cyclosporin A in rheumatoid arthritis : worldwide experience. *Br J Rheum* 1993;**32**(suppl 1):57-9.

Gepner 1989

Gepner, Amor B, Fournier C. 1.25. hydroxy vitamin D3 potentiates the in vitro inhibitory effects of cyclosporine A on T cells from rheumatoid arthritis patients. *Arthritis Rheum* 1989;**22**:31-4.

Hess 1982

Hess A, Turschka P, Pu Z, et al. Effects of cyclosporine A on human lymphocyte response in vitro. *J Immunol* 1982;**128**:360-7.

Intl consensus 1993

An International consensus report : the use of cyclosporin A in rheumatoid arthritis. *Br J Rheum* 1993;**32**(suppl 1):1-3.

Jadad 1996

Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized trials: is blinding necessary?. *Control Clin Trial* 1996;**17**:1-12.

Kruger 1992

Kruger K, Schattenkirchner M. Cyclosporine versus azathioprine in the treatment of rheumatoid arthritis ; results of a controlled double blind multicenter study(abstract). *J Autoimmun* 1992;**5, xix**.

OMERACT 1993

OMERACT. Conference on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *J Rheumatol* 1993;**20**:526-91.

Van Rijthoven 1991

Van Rijthoven AW, Dijkmans BA, Goei The HS, et al. Comparison of cyclosporine and D penicillamine for rheumatoid arthritis : a randomized double blind multicenter study. *J Rheumatol* 1991;**18**:815-20.

Waalen 1987

Waalen K, Forre O, Linker M, et al. Evidence of an activated T cell system with augmented turn over of interleukin 2 in rheumatoid arthritis. *Scand J Immunol* 1987;**25**:367-73.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dougados 1988

Methods	Randomized Double blind Placebo controlled Sample size at entry : cyclo : 26; placebo : 26. Study duration : 16 weeks
Participants	Patients with active RA (ARA definite or classic) Setting : clinic outpatients Mean age (yrs) : 57.5 Sex : F/M : cyclo ; 23/3; placebo : 24/2

Dougados 1988 *(Continued)*

	Disease duration : cyclo : 8.0; placebo : 15.0
Interventions	Cyclosporine twice daily at 5mg/kg/day or 2.5 mg/kg/day for those concurrently taking cimetidine. Dose reduced by half if renal toxicity appeared (defined as >50% increase in plasma creatinine level over baseline), halved again if toxicity persists 1 wk later and discontinued if toxicity persists 1 wk after 2nd reduction. Placebo
Outcomes	Pain Ritchie index Morning stiffness duration Swollen joint PIP circumference Grip strengh Lee functional index Patient global assessment ESR CRP
Notes	Quality score : 4 Concealment of allocation : B

Risk of bias

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

Forre 1994

Methods	Randomized Double blind Placebo controlled Sample size at entry : cyclo : 61; placebo : 61. Study duration : 48 weeks
Participants	Patients with active RA Setting : multicenter study (6) Mean age (yrs) : cyclo :52.4; placebo 50.3 Sex % F : cyclo : 68; placebo : 67 Disease duration : cyclo : 8.8; placebo : 8.1
Interventions	Cyclosporine twice daily, 5mg/kg/day; Dose reduced by half if toxicity appeared (defined as serum creatinine >50% above baseline or > 150 umol/L, increase in bilirubin or transaminse levels twice upper limit of normal or increase in serum potassium above upper limit), halved again if toxicity persisted 2 wks later and discontinued if toxicity persisted 2 wks after second reduction. Placebo
Outcomes	Pain Ritchie index Morning stiffness duration Swollen joint PIP circumference Grip strengh Lee functional index Patient globall assessment

Forre 1994 *(Continued)*

	Physician global assessment ESR CRP Larsen score Number of erosions
Notes	Quality score : 5 Concealment of allocation : B

Risk of bias

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

Tugwell 1990

Methods	Randomized Double blind Placebo controlled Sample size at entry : cyclo : 72; placebo : 72. Study duration : 24 weeks
Participants	Patients with active RA (ARA definite or classic) Setting : clinic outpatients; multicenter study Mean age (yrs) : cyclo : 54.4; placebo : 55.2 Sex % : cyclo ; 72; placebo : 69 Disease duration : cyclo : 10.9; placebo : 11.1
Interventions	Cyclosporine twice daily, dose 2.5 mg/kg/day; Dose increased weekly by 25% until serum trough levels of cyclosporine of 75-150 ng/mL achieved unless prevented by >50% in serum creatinine; Dose reduced by 25-50% if a) Toxicity found (measured by serum creatinine increase to baseline value + 75% or if >150 micromol/L) b) Trough serum cyclosporine levels >150 ng/mL c) Serum AST, alkaline phosphatase, serum potassium, blood pressure abnormal Placebo
Outcomes	Pain Morning stiffness duration Swollen joint Grip strengh ESR Patient global assessment Physician global assessment
Notes	Quality score : 4 Concealment of allocation : B

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
Van Rijthoven 1986	This study was excluded because of the high dose of cyclosporine (10 mg/kg/day).

DATA AND ANALYSES

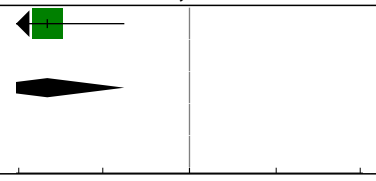
Comparison 1. Cyclosporine vs placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in number of tender joints	1	144	Mean Difference (IV, Fixed, 95% CI)	-8.20 [-12.64, -3.76]
2 Change in number of swollen joints	3	312	Mean Difference (IV, Fixed, 95% CI)	-3.19 [-4.29, -2.10]
3 Change in patient overall assessment	2	266	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.25, 0.41]
4 Change in physician overall assessment	2	266	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.02, 0.69]
5 Acute phase reactants	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Change in ESR	3	312	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-5.17, 4.85]
5.2 Change in CRP	1	122	Mean Difference (IV, Fixed, 95% CI)	-18.4 [-53.11, 16.31]
6 Radiologic evaluation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Change in larsen score	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.30, -0.06]
6.2 Change in erosion score	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.87, -0.07]
7 Index scores	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Change in Lee functional index	2	168	Mean Difference (IV, Fixed, 95% CI)	-3.74 [-5.16, -2.33]
7.3 Change in problem elicitation technique (PET)	1	144	Mean Difference (IV, Fixed, 95% CI)	-20.7 [-175.98, 134.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Change in duration of morning stiffness	3	312	Mean Difference (IV, Fixed, 95% CI)	-54.31 [-90.37, -18.25]
9 Change in Grip Strength	3	312	Mean Difference (IV, Fixed, 95% CI)	16.39 [5.19, 27.60]
10 Change in PIP circumference	2	168	Mean Difference (IV, Fixed, 95% CI)	-6.17 [-9.89, -2.44]
11 Change in Ritchie Joint Score	2	168	Mean Difference (IV, Fixed, 95% CI)	-5.11 [-8.20, -2.02]
12 Pain scores	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Change in pain (10 cm VAS)	2	190	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.32, -0.57]
12.2 Change in pain (1-max pain to 4-no pain, Likert scale)	1	122	Mean Difference (IV, Fixed, 95% CI)	0.4 [0.12, 0.68]

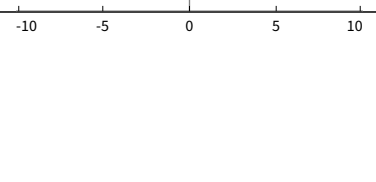
Analysis 1.1. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 1 Change in number of tender joints.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tugwell 1990	72	-9.4 (14.4)	72	-1.2 (12.7)		100%	-8.2[-12.64,-3.76]
Total ***	**72**		**72**			**100%**	**-8.2[-12.64,-3.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.62(P=0)							



Analysis 1.2. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 2 Change in number of swollen joints.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dougados 1988	22	-3.4 (4.6)	24	2.1 (6.2)		12.08%	-5.44[-8.59,-2.29]
Tugwell 1990	72	-3.2 (5.9)	72	-0.9 (5.1)		36.78%	-2.3[-4.11,-0.49]
Forre 1994	61	-3.6 (4.7)	61	-0.3 (3.9)		51.14%	-3.3[-4.83,-1.77]
Total ***	**155**		**157**			**100%**	**-3.19[-4.29,-2.1]**
Heterogeneity: Tau^2=0; Chi^2=2.91, df=2(P=0.23); I^2=31.25%							
Test for overall effect: Z=5.71(P<0.0001)							



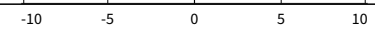
Analysis 1.3. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 3 Change in patient overall assessment.

Study or subgroup	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tugwell 1990	72	2.1 (0.9)	72	2.9 (1.7)	56.63%	-0.8[-1.24,-0.36]
Forre 1994	61	2 (1.6)	61	0.8 (1.3)	43.37%	1.23[0.73,1.73]
Total * **	**133**		**133**		**100%**	**0.08[-0.25,0.41]**
Heterogeneity: Tau^2=0; Chi^2=35.62, df=1(P<0.0001); I^2=97.19%						
Test for overall effect: Z=0.48(P=0.63)						

Favours Treatment Favours Control

Analysis 1.4. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 4 Change in physician overall assessment.

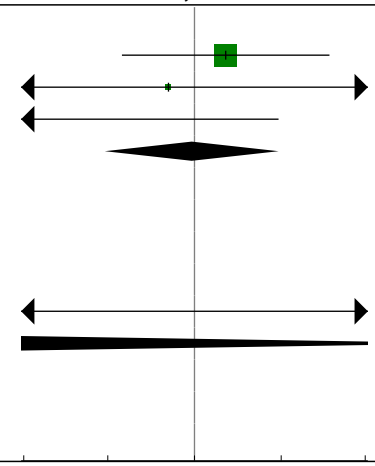
Study or subgroup	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tugwell 1990	72	2.1 (1.7)	72	2.9 (1.7)	40.83%	-0.8[-1.36,-0.24]
Forre 1994	61	1.8 (1.5)	61	0.7 (1.1)	59.17%	1.12[0.66,1.58]
Total * **	**133**		**133**		**100%**	**0.34[-0.02,0.69]**
Heterogeneity: Tau^2=0; Chi^2=27.17, df=1(P<0.0001); I^2=96.32%						
Test for overall effect: Z=1.86(P=0.06)						



Favours Treatment Favours Control

Analysis 1.5. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 5 Acute phase reactants.

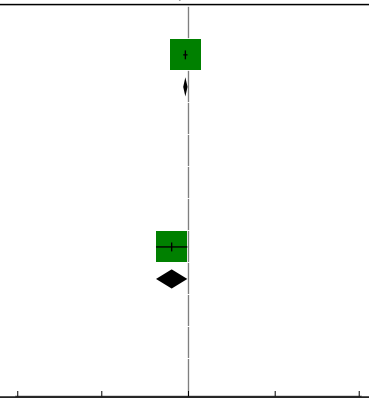
Study or subgroup	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Change in ESR					
Tugwell 1990	72	-1.6 (13.6)	72	-3.4 (22.1)	70.18%	1.8[-4.18,7.78]
Forre 1994	61	-3.5 (36.7)	61	-2 (30.5)	17.53%	-1.5[-13.47,10.47]
Dougados 1988	22	-8.9 (28.4)	24	0.5 (19.9)	12.29%	-9.45[-23.75,4.85]
Subtotal * **	**155**		**157**		**100%**	**-0.16[-5.17,4.85]**
Heterogeneity: Tau^2=0; Chi^2=2.08, df=2(P=0.35); I^2=3.95%						
Test for overall effect: Z=0.06(P=0.95)						
1.5.2 Change in CRP						
Forre 1994	61	-13.4 (62.5)	61	5 (123.4)	100%	-18.4[-53.11,16.31]
Subtotal * **	**61**		**61**		**100%**	**-18.4[-53.11,16.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.04(P=0.3)						
Test for subgroup differences: Chi^2=1.04, df=1 (P=0.31), I^2=3.75%						



Favours Treatment Favours Control

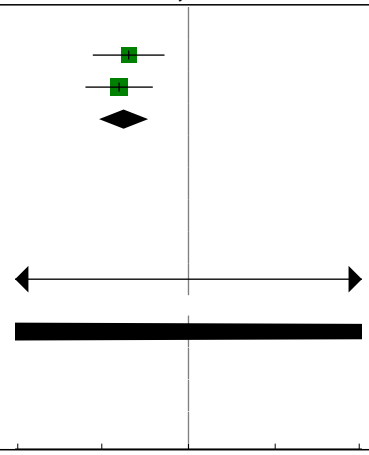
Analysis 1.6. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 6 Radiologic evaluation.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 Change in larsen score							
Forre 1994	37	-0 (0.2)	23	0.2 (0.2)		100%	-0.18[-0.3,-0.06]
Subtotal ***	**37**		**23**			**100%**	**-0.18[-0.3,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.82(P=0)							
1.6.2 Change in erosion score							
Forre 1994	37	0.1 (1.8)	23	1 (1.7)		100%	-0.97[-1.87,-0.07]
Subtotal ***	**37**		**23**			**100%**	**-0.97[-1.87,-0.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.04)							
Test for subgroup differences: Chi^2=2.89, df=1 (P=0.09), I^2=65.34%							



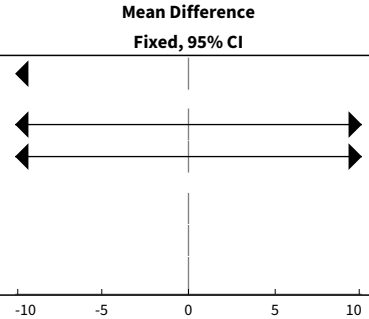
Analysis 1.7. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 7 Index scores.

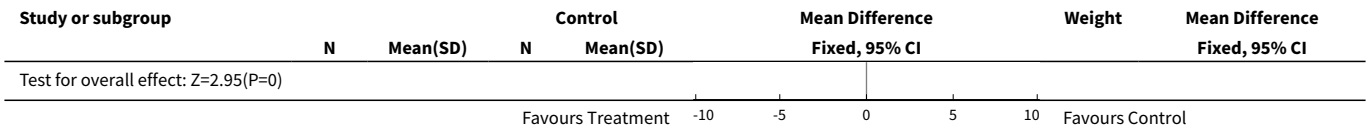
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 Change in Lee functional index							
Dougados 1988	22	-3.9 (3)	24	-0.5 (4.1)		46.87%	-3.45[-5.52,-1.38]
Forre 1994	61	-2.2 (5.5)	61	1.8 (5.5)		53.13%	-4[-5.94,-2.06]
Subtotal ***	**83**		**85**			**100%**	**-3.74[-5.16,-2.33]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=5.18(P<0.0001)							
1.7.3 Change in problem elicitation technique (PET)							
Tugwell 1990	72	-44.9 (450.6)	72	-24.2 (498.9)		100%	-20.7[-175.98,134.58]
Subtotal ***	**72**		**72**			**100%**	**-20.7[-175.98,134.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.79)							
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%							



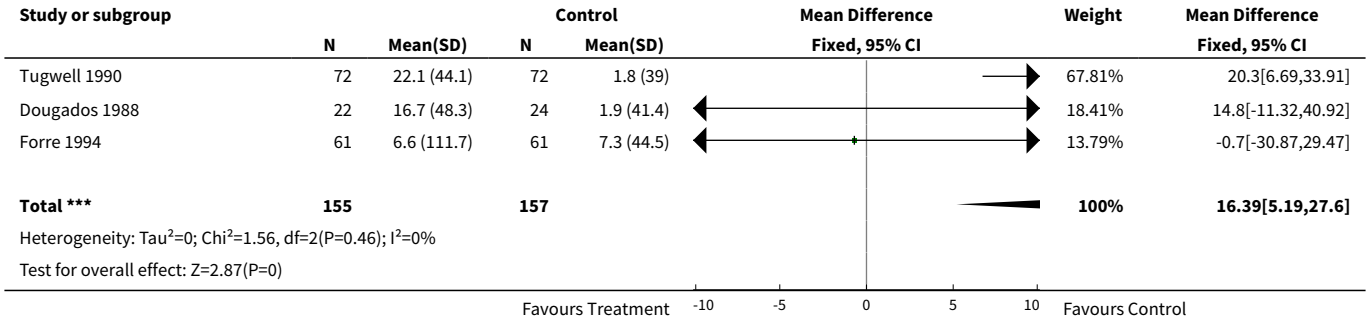
Analysis 1.8. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 8 Change in duration of morning stiffness.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dougados 1988	22	-108 (112.2)	24	-11.7 (146.1)		23.16%	-96.38[-171.31,-21.45]
Tugwell 1990	72	-102 (254.4)	72	-30 (305.4)		15.43%	-72[-163.81,19.81]
Forre 1994	61	-46.2 (132)	61	-12.2 (127.3)		61.41%	-34[-80.02,12.02]
Total ***	**155**		**157**			**100%**	**-54.31[-90.37,-18.25]**
Heterogeneity: Tau^2=0; Chi^2=2.1, df=2(P=0.35); I^2=4.85%							

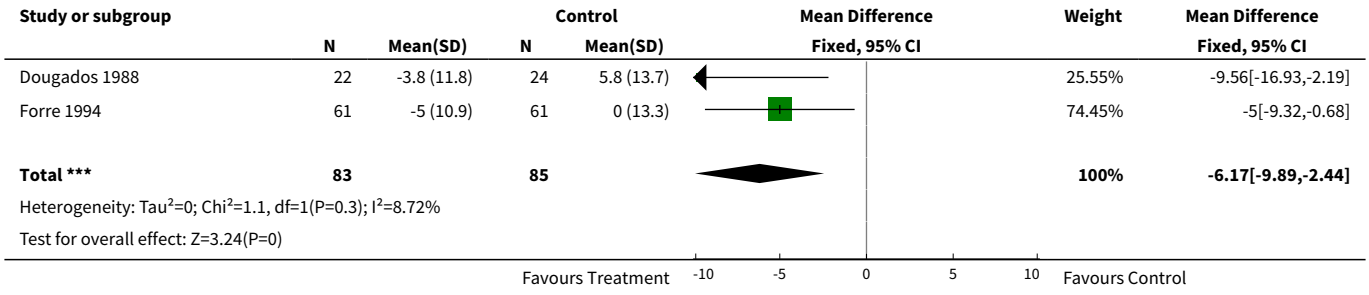




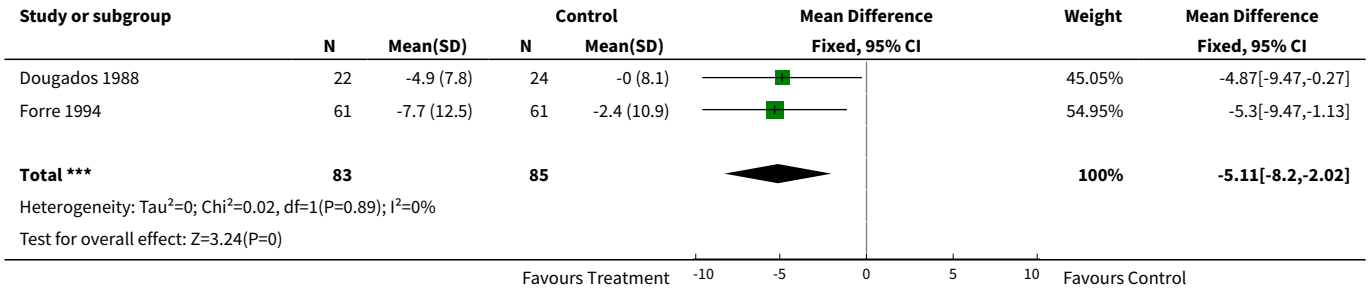
Analysis 1.9. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 9 Change in Grip Strength.



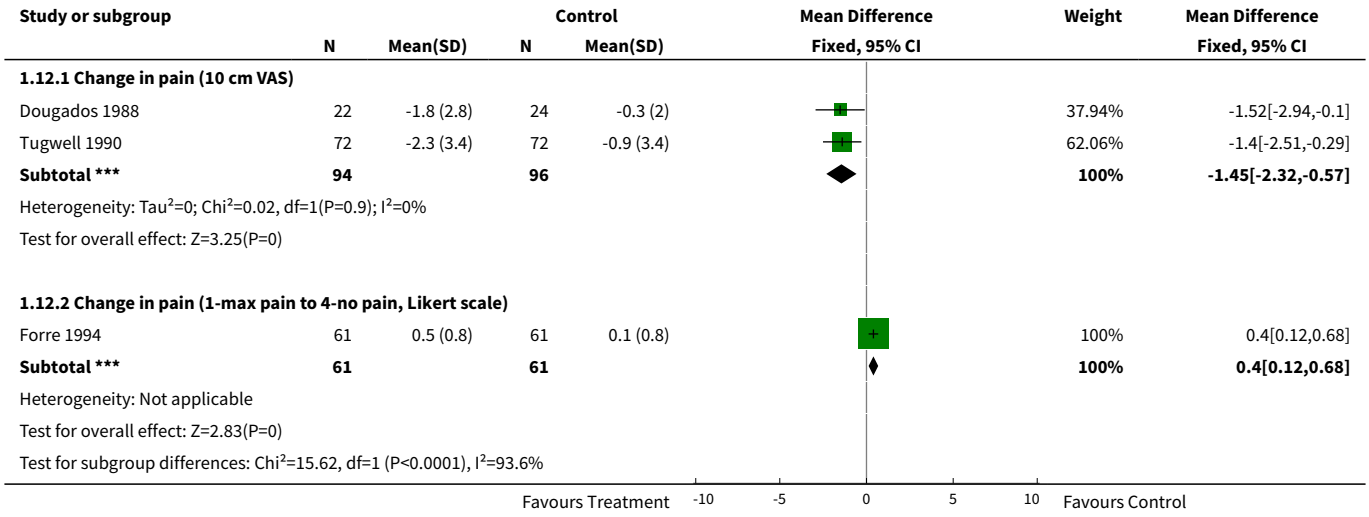
Analysis 1.10. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 10 Change in PIP circumference.



Analysis 1.11. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 11 Change in Ritchie Joint Score.



Analysis 1.12. Comparison 1 Cyclosporine vs placebo - Efficacy, Outcome 12 Pain scores.

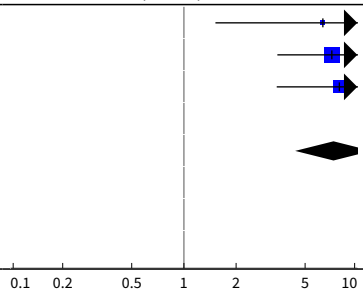


Comparison 2. Cyclosporine vs placebo - Toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypertrichosis	3	318	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.29 [4.38, 12.12]
2 Headache	1	122	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.31 [1.05, 10.39]
3 Tremor	2	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.29 [2.84, 9.86]
4 Dyspepsia	3	318	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.01 [1.13, 3.59]
5 Nausea	3	318	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.24, 3.81]
6 Paraesthesia	3	318	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.34 [1.12, 4.88]
7 Flushing	1	122	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [0.53, 7.89]
8 Diarrhea	2	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.57, 3.08]
9 Gum hyperplasia	2	196	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.97 [2.11, 30.16]
10 Gastric ulceration	1	52	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
11 Mammary hypertrophy	1	52	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]

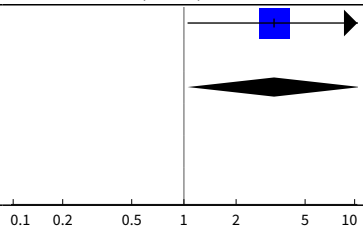
Analysis 2.1. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 1 Hypertrichosis.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Dougados 1988	8/26	1/26		12.77%	6.33[1.52,26.26]
Tugwell 1990	35/72	6/72		49.71%	7.13[3.46,14.66]
Forre 1994	26/61	3/61		37.52%	7.88[3.43,18.07]
Total (95% CI)	**159**	**159**		**100%**	**7.29[4.38,12.12]**
Total events: 69 (Treatment), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=7.65(P<0.0001)					



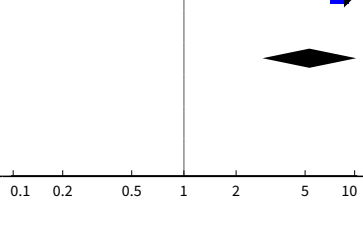
Analysis 2.2. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 2 Headache.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Forre 1994	10/61	3/61		100%	3.31[1.05,10.39]
Total (95% CI)	**61**	**61**		**100%**	**3.31[1.05,10.39]**
Total events: 10 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.05(P=0.04)					



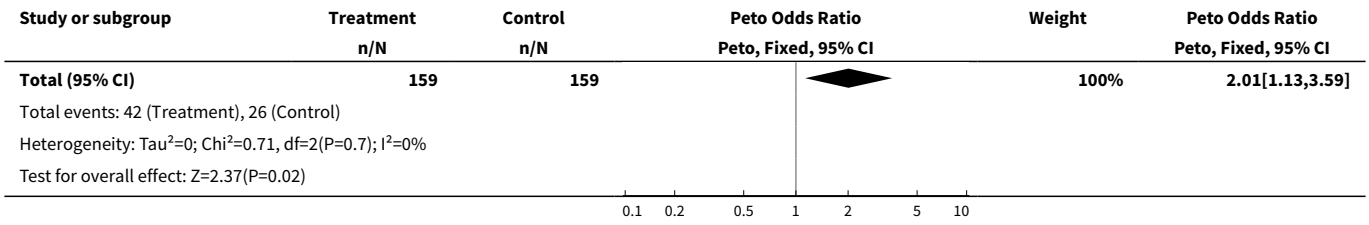
Analysis 2.3. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 3 Tremor.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Tugwell 1990	15/72	5/72		43.76%	3.17[1.24,8.12]
Forre 1994	26/61	3/61		56.24%	7.88[3.43,18.07]
Total (95% CI)	**133**	**133**		**100%**	**5.29[2.84,9.86]**
Total events: 41 (Treatment), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.02, df=1(P=0.16); I^2=50.54%					
Test for overall effect: Z=5.24(P<0.0001)					

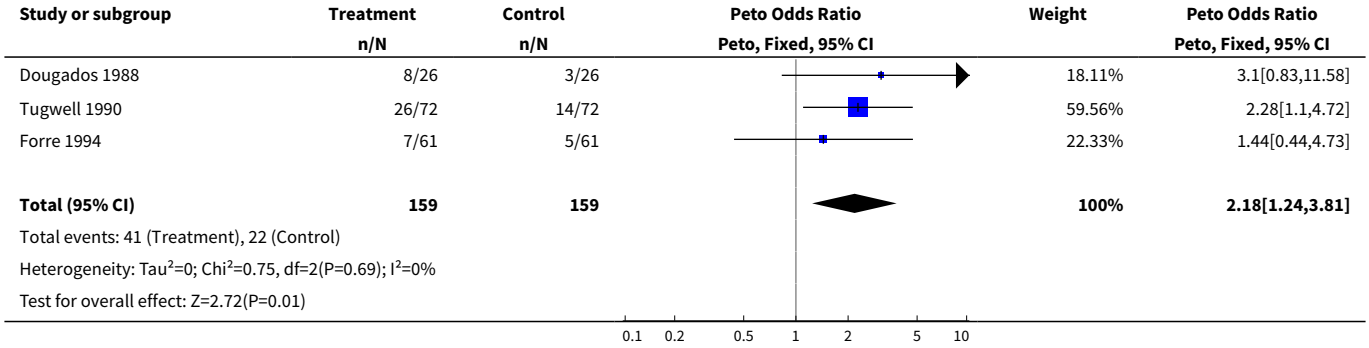


Analysis 2.4. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 4 Dyspepsia.

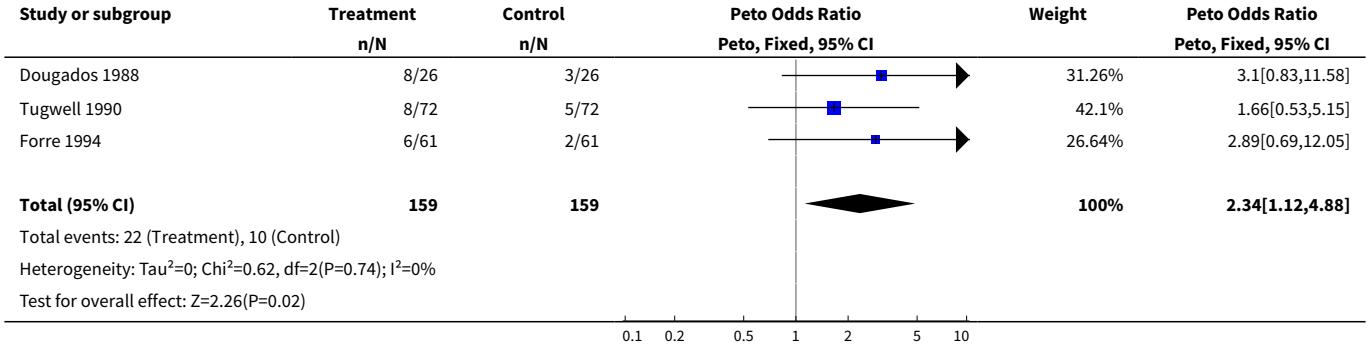
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Tugwell 1990	34/72	22/72		75.3%	2.01[1.03,3.91]
Dougados 1988	2/26	2/26		8.23%	1[0.13,7.54]
Forre 1994	6/61	2/61		16.47%	2.89[0.69,12.05]



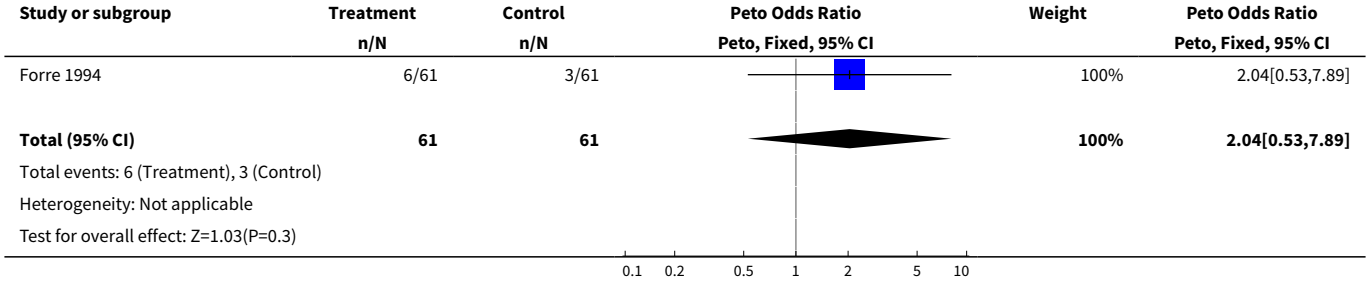
Analysis 2.5. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 5 Nausea.



Analysis 2.6. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 6 Paraesthesia.

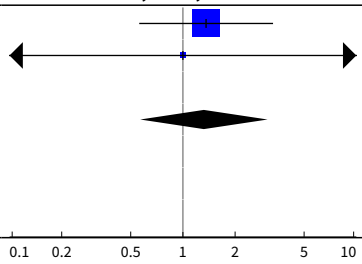


Analysis 2.7. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 7 Flushing.



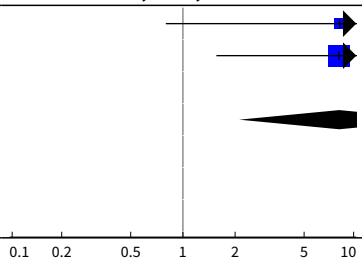
Analysis 2.8. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 8 Diarrhea.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Tugwell 1990	13/72	10/72		90.75%	1.36[0.56,3.31]
Forre 1994	1/61	1/61		9.25%	1[0.06,16.17]
Total (95% CI)	**133**	**133**		**100%**	**1.32[0.57,3.08]**
Total events: 14 (Treatment), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=0.65(P=0.52)					



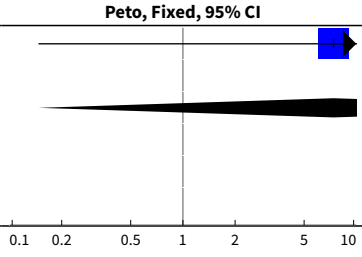
Analysis 2.9. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 9 Gum hyperplasia.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Dougados 1988	3/26	0/26		33.24%	8.02[0.8,80.68]
Tugwell 1990	6/72	0/72		66.76%	7.94[1.56,40.51]
Total (95% CI)	**98**	**98**		**100%**	**7.97[2.11,30.16]**
Total events: 9 (Treatment), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=3.06(P=0)					



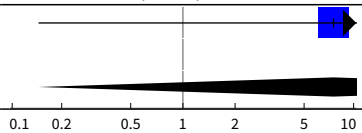
Analysis 2.10. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 10 Gastric ulceration.

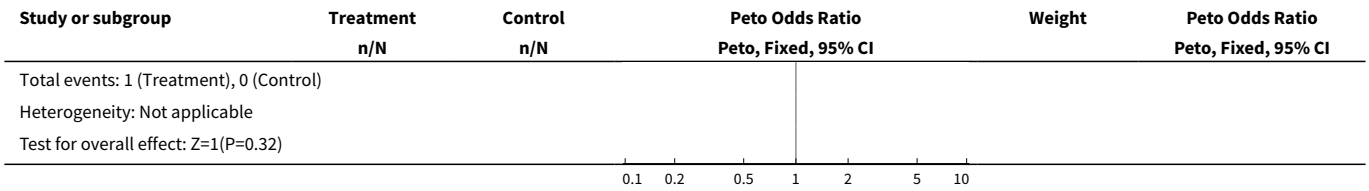
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Dougados 1988	1/26	0/26		100%	7.39[0.15,372.38]
Total (95% CI)	**26**	**26**		**100%**	**7.39[0.15,372.38]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					



Analysis 2.11. Comparison 2 Cyclosporine vs placebo - Toxicity, Outcome 11 Mammary hypertrophy.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Dougados 1988	1/26	0/26		100%	7.39[0.15,372.38]
Total (95% CI)	**26**	**26**		**100%**	**7.39[0.15,372.38]**





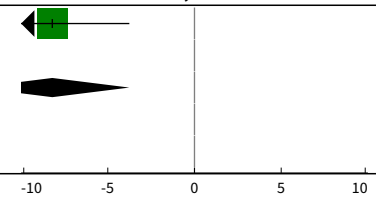
Comparison 3. Cyclosporine vs placebo - Efficacy-12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in number of tender joints	1	144	Mean Difference (IV, Fixed, 95% CI)	-8.20 [-12.64, -3.76]
2 Change in number of swollen joints	3	312	Mean Difference (IV, Fixed, 95% CI)	-3.19 [-4.29, -2.10]
3 Change in patient overall assessment	2	266	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.25, 0.41]
4 Change in physician overall assessment	2	266	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.02, 0.69]
5 Acute phase reactants	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Change in ESR	3	312	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-5.17, 4.85]
5.2 Change in CRP	1	122	Mean Difference (IV, Fixed, 95% CI)	-18.4 [-53.11, 16.31]
6 Radiologic evaluation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Change in larsen score	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.30, -0.06]
6.2 Change in erosion score	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.87, -0.07]
7 Index scores	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Change in Lee functional index	2	168	Mean Difference (IV, Fixed, 95% CI)	-3.74 [-5.16, -2.33]
7.3 Change in problem elicitation technique (PET)	1	144	Mean Difference (IV, Fixed, 95% CI)	-20.7 [-175.98, 134.58]
8 Change in duration of morning stiffness	3	312	Mean Difference (IV, Fixed, 95% CI)	-54.31 [-90.37, -18.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Change in Grip Strength	3	312	Mean Difference (IV, Fixed, 95% CI)	16.39 [5.19, 27.60]
10 Change in PIP circumference	2	168	Mean Difference (IV, Fixed, 95% CI)	-6.17 [-9.89, -2.44]
11 Change in Ritchie Joint Score	2	168	Mean Difference (IV, Fixed, 95% CI)	-5.11 [-8.20, -2.02]
12 Pain scores	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Change in pain (10 cm VAS)	2	190	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.32, -0.57]
12.2 Change in pain (1-max pain to 4-no pain, Likert scale)	1	122	Mean Difference (IV, Fixed, 95% CI)	0.4 [0.12, 0.68]

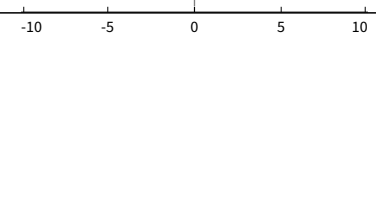
Analysis 3.1. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 1 Change in number of tender joints.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tugwell 1990	72	-9.4 (14.4)	72	-1.2 (12.7)		100%	-8.2[-12.64,-3.76]
Total ***	**72**		**72**			**100%**	**-8.2[-12.64,-3.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.62(P=0)							



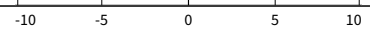
Analysis 3.2. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 2 Change in number of swollen joints.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tugwell 1990	72	-3.2 (5.9)	72	-0.9 (5.1)		36.78%	-2.3[-4.11,-0.49]
Dougados 1988	22	-3.4 (4.6)	24	2.1 (6.2)		12.08%	-5.44[-8.59,-2.29]
Forre 1994	61	-3.6 (4.7)	61	-0.3 (3.9)		51.14%	-3.3[-4.83,-1.77]
Total ***	**155**		**157**			**100%**	**-3.19[-4.29,-2.1]**
Heterogeneity: Tau^2=0; Chi^2=2.91, df=2(P=0.23); I^2=31.25%							
Test for overall effect: Z=5.71(P<0.0001)							



Analysis 3.3. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 3 Change in patient overall assessment.

Study or subgroup	Control				Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Tugwell 1990	72	2.1 (0.9)	72	2.9 (1.7)		56.63%	-0.8[-1.24,-0.36]
Forre 1994	61	2 (1.6)	61	0.8 (1.3)		43.37%	1.23[0.73,1.73]
Total ***	**133**		**133**			**100%**	**0.08[-0.25,0.41]**
Heterogeneity: Tau^2=0; Chi^2=35.62, df=1(P<0.0001); I^2=97.19%							
Test for overall effect: Z=0.48(P=0.63)							

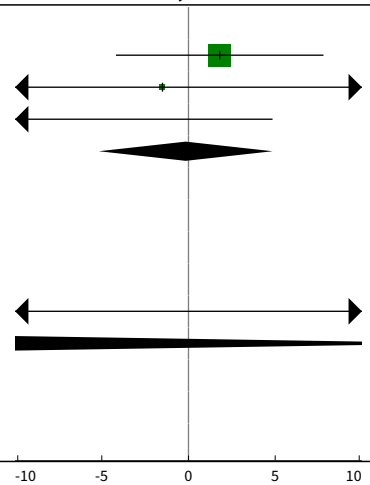


Analysis 3.4. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 4 Change in physician overall assessment.

Study or subgroup	Control				Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Tugwell 1990	72	2.1 (1.7)	72	2.9 (1.7)		40.83%	-0.8[-1.36,-0.24]
Forre 1994	61	1.8 (1.5)	61	0.7 (1.1)		59.17%	1.12[0.66,1.58]
Total ***	**133**		**133**			**100%**	**0.34[-0.02,0.69]**
Heterogeneity: Tau^2=0; Chi^2=27.17, df=1(P<0.0001); I^2=96.32%							
Test for overall effect: Z=1.86(P=0.06)							

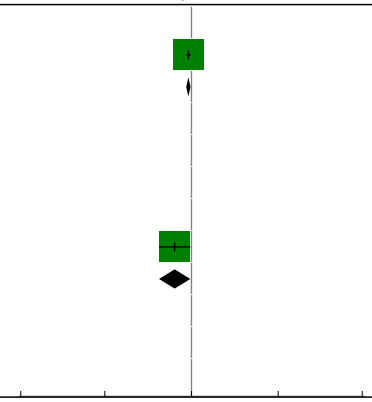
Analysis 3.5. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 5 Acute phase reactants.

Study or subgroup	Control				Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
3.5.1 Change in ESR							
Tugwell 1990	72	-1.6 (13.6)	72	-3.4 (22.1)		70.18%	1.8[-4.18,7.78]
Forre 1994	61	-3.5 (36.7)	61	-2 (30.5)		17.53%	-1.5[-13.47,10.47]
Dougados 1988	22	-8.9 (28.4)	24	0.5 (19.9)		12.29%	-9.45[-23.75,4.85]
Subtotal ***	**155**		**157**			**100%**	**-0.16[-5.17,4.85]**
Heterogeneity: Tau^2=0; Chi^2=2.08, df=2(P=0.35); I^2=3.95%							
Test for overall effect: Z=0.06(P=0.95)							
3.5.2 Change in CRP							
Forre 1994	61	-13.4 (62.5)	61	5 (123.4)		100%	-18.4[-53.11,16.31]
Subtotal ***	**61**		**61**			**100%**	**-18.4[-53.11,16.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.04(P=0.3)							
Test for subgroup differences: Chi^2=1.04, df=1 (P=0.31), I^2=3.75%							



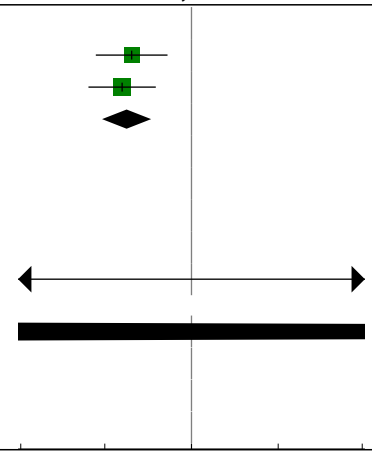
Analysis 3.6. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 6 Radiologic evaluation.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.6.1 Change in larsen score							
Forre 1994	37	-0 (0.2)	23	0.2 (0.2)		100%	-0.18[-0.3,-0.06]
Subtotal ***	**37**		**23**			**100%**	**-0.18[-0.3,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.82(P=0)							
3.6.2 Change in erosion score							
Forre 1994	37	0.1 (1.8)	23	1 (1.7)		100%	-0.97[-1.87,-0.07]
Subtotal ***	**37**		**23**			**100%**	**-0.97[-1.87,-0.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.04)							
Test for subgroup differences: Chi^2=2.89, df=1 (P=0.09), I^2=65.34%							



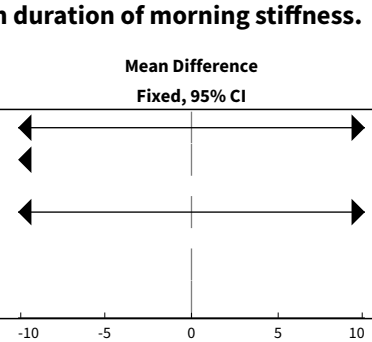
Analysis 3.7. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 7 Index scores.

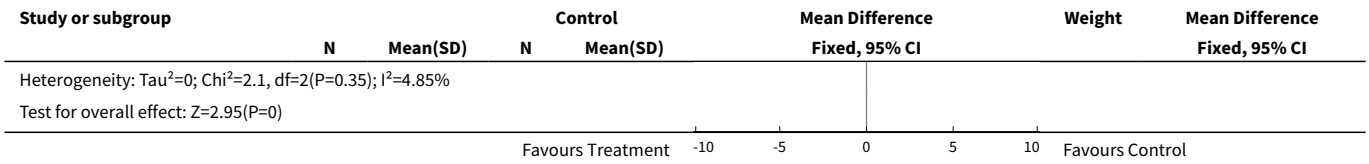
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.7.1 Change in Lee functional index							
Dougados 1988	22	-3.9 (3)	24	-0.5 (4.1)		46.87%	-3.45[-5.52,-1.38]
Forre 1994	61	-2.2 (5.5)	61	1.8 (5.5)		53.13%	-4[-5.94,-2.06]
Subtotal ***	**83**		**85**			**100%**	**-3.74[-5.16,-2.33]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=5.18(P<0.0001)							
3.7.3 Change in problem elicitation technique (PET)							
Tugwell 1990	72	-44.9 (450.6)	72	-24.2 (498.9)		100%	-20.7[-175.98,134.58]
Subtotal ***	**72**		**72**			**100%**	**-20.7[-175.98,134.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.79)							
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%							



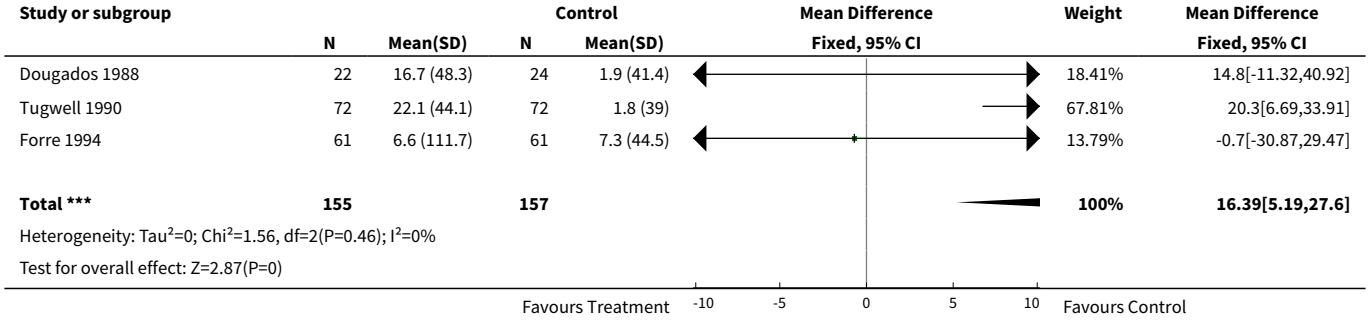
Analysis 3.8. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 8 Change in duration of morning stiffness.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tugwell 1990	72	-102 (254.4)	72	-30 (305.4)		15.43%	-72[-163.81,19.81]
Dougados 1988	22	-108 (112.2)	24	-11.7 (146.1)		23.16%	-96.38[-171.31,-21.45]
Forre 1994	61	-46.2 (132)	61	-12.2 (127.3)		61.41%	-34[-80.02,12.02]
Total ***	**155**		**157**			**100%**	**-54.31[-90.37,-18.25]**

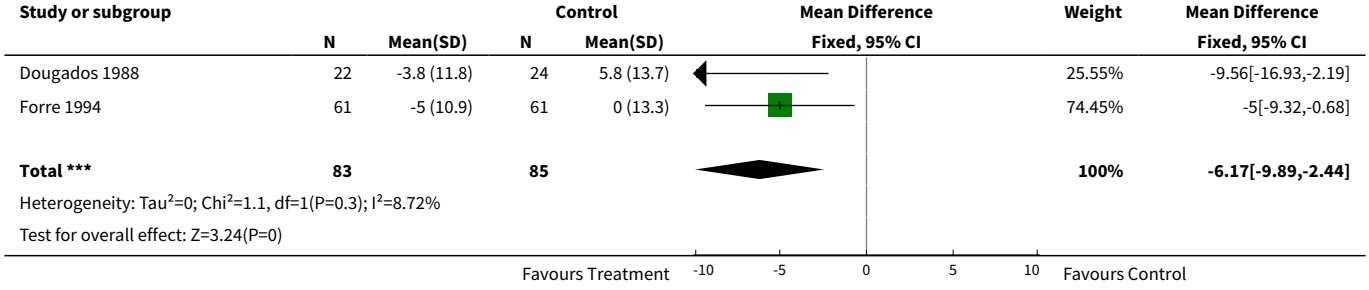




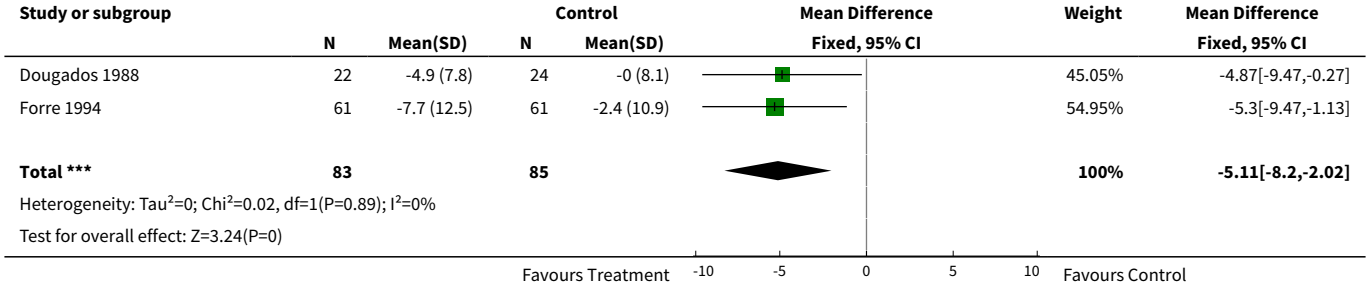
Analysis 3.9. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 9 Change in Grip Strength.



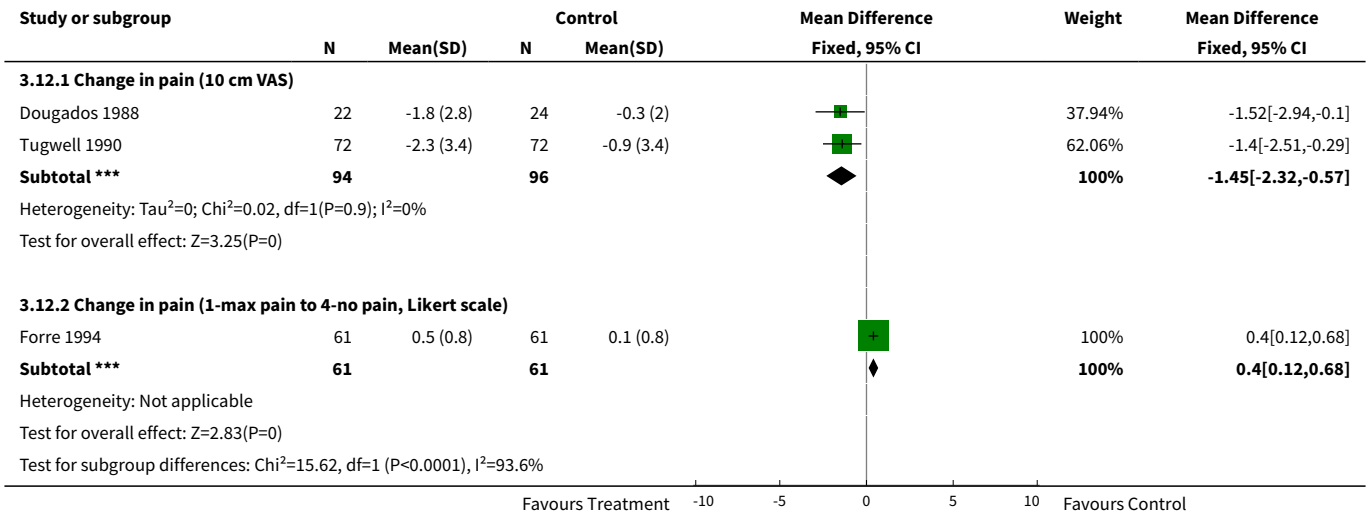
Analysis 3.10. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 10 Change in PIP circumference.



Analysis 3.11. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 11 Change in Ritchie Joint Score.



Analysis 3.12. Comparison 3 Cyclosporine vs placebo - Efficacy-12 months, Outcome 12 Pain scores.



WHAT'S NEW

Date	Event	Description
28 May 2008	Amended	Converted to new review format. CMSG ID C098-R

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Clinical Epidemiology Unit, University of Ottawa, Ontario, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Cyclosporine [*therapeutic use]

MeSH check words

Humans