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Cyclosporin as an oral corticosteroid sparing agent in stable asthma.
Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002993.
DOI: 10.1002/14651858.CD002993.

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[Intervention Review]

Cyclosporin as an oral corticosteroid sparing agent in stable asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2010.

Citation: Evans DJ, Cullinan P, Geddes DM, Walters EH, Milan SJ, Jones P. Cyclosporin as an oral corticosteroid sparing agent in stable asthma. *Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No.: CD002993. DOI: 10.1002/14651858.CD002993.

ABSTRACT

Background

Patients with chronic severe asthma are often dependent on the long term prescription of oral corticosteroids. The use of steroids is associated with serious side effects. Physicians treating such patients continue to search for alternative therapies that reduce the need for chronic dosing with oral steroids. Cyclosporin is an immunosuppressive agent and has benefits in the treatment of a number of inflammatory disorders. It has therefore been identified as an potentially useful agent in the treatment of chronic severe asthma both in terms of possible efficacy and as a steroid sparing agent.

Objectives

The objective of this review was to assess the effects of adding cyclosporin to oral steroids in the treatment of chronic steroid dependent asthmatics.

Search methods

The Cochrane Airways Group Specialised Register and reference lists of identified articles were searched. The most recent search was conducted in September 2010.

Selection criteria

Randomised trials looking at the addition of cyclosporin compared to placebo in adult steroid dependent asthmatics.

Data collection and analysis

Trial quality was assessed and data extraction was carried out by two reviewers independently. Study authors were contacted for missing information.

Main results

Three trials fulfilled the criteria for inclusion in the review and a total of 106 patients were recruited into these studies. Data from 98 patients could be analysed. There was a small but significant treatment effect for cyclosporin in terms of steroid dose reduction (SMD -0.5, 95% CI -1.0, -0.04). No meta-analyses could be performed for measures of lung function although one study showed small, but significant improvements in lung spirometry.

Authors' conclusions

The changes with cyclosporin are small and of questionable clinical significance. Given the side effects of cyclosporin, the evidence available does not recommend routine use of this drug in the treatment of oral corticosteroid dependent asthma.

PLAIN LANGUAGE SUMMARY

Cyclosporin (the drug for preventing organ rejection after transplant) as an oral corticosteroid sparing agent in stable asthma

Some people with asthma need to rely on corticosteroid drugs to control their asthma. Corticosteroids help reduce the inflammation (swelling) of the airways (passages to the lungs) associated with asthma. Long-term use of these drugs may have serious adverse effects, so other ways to try and cut down on the need for corticosteroids are sometimes tried. Cyclosporin is the drug used to prevent organ rejections after transplants, and it can be used for other conditions involving inflammation (such as arthritis). The review of trials found that cyclosporin has a small impact on asthma symptoms, but it has major serious adverse effects.

BACKGROUND

The recognition that asthma is a consequence of airways inflammation has focused treatment objectives towards anti-inflammatory agents. Inhaled and systemic corticosteroids are of proven benefit.

There are, however, a group of asthmatics who continue to have symptoms despite high doses of inhaled steroids and require maintenance treatment with oral corticosteroids. Whilst these patients are in the minority, in the order of 1-2%, this subset constitute a significant number and consume a considerable and disproportionate fraction of the health care resources. Furthermore these patients are at risks from the unwanted effects of long term treatment with systemic corticosteroids. These include osteoporosis, diabetes, hypertension, neuropsychiatric disorders and growth retardation in children.

As a result of this clinical dilemma there have been a number of clinical trials examining the use of 'second-line' immunosuppressive agents. These include agents such as methotrexate, gold, azathioprine and cyclosporin A. The concept that these drugs may be of benefit in asthma has arisen from studies showing there are benefits in other inflammatory conditions such as rheumatoid arthritis. To date only methotrexate in asthma has been reviewed.

Cyclosporin is a cyclic undecapeptide metabolite extracted from the fungus Tolypocyladium inflatum. It is used for the prevention of allograft rejection and has also been found to be effective in the treatment of a variety of inflammatory disorders inclusive of psoriasis, lichen planus, nephrotic syndrome and rheumatoid arthritis. Cyclosporin acts by inhibiting inflammatory cells, predominantly lymphocytes, but also eosinophils and mast cells. At a cellular level cyclosporin binds cytosolic proteins, for example cyclophilin, whose roles include regulation of protein kinases, phospholipase A2 and post-translational folding of proteins. It also binds to pro-inflammatory transcriptional factors such as activator protein 3 (AP3) and nuclear factor kB (NFkB). Additionally cyclosporin blocks the membrane receptor for interleukin-1 (IL-1).

Through these effects cyclosporin has been specifically shown to:

1. inhibit mast cell and basophil secretion of leukotriene C4 (LTC4), platelet activating factor (PAF), and histamine
2. inhibit lymphocyte synthesis of cytokines, for example IL-1, IL-2, IL-3, IL-4, IL-5, GM-CSF
3. reduce B cell IL-4 stimulated IgE synthesis
4. inhibit eosinophil function
5. block macrophage respiratory burst oxidase activation and IL-1 production.

Further to these studies showing the immunosuppressive effects of cyclosporin there are other data demonstrating an added and superior inhibitory effect of this drug compared to glucocorticoids on lymphocytes of asthmatic subjects. Thus there is laboratory evidence to support the use of cyclosporin in asthma particularly as activated lymphocytes have been shown to correlate with disease severity in asthma.

Despite the potential benefits of cyclosporin in asthma there are established side effects of the drug that may preclude its use in particular impairment of renal function and hypertension. Other documented toxic effects include elevations of liver enzymes, hypertrichosis, neuropathy/paraesthesia and gastrointestinal disturbances.

Cyclosporin is given by both orally and intravenously. The usual dose range is 3 to 7.5 mg/kg body weight. Treatment should be monitored and drug maintained at levels of 80 - 150 ng/ml.

The use of cyclosporin as an adjunct to oral corticosteroids has been reported in both open & blinded randomised controlled studies in asthma. These studies have employed differing methodology and to date the results have been conflicting. Previous narrative reviews give the overall impression that cyclosporin is of benefit, but this has not been established. A systematic review with meta-analysis may help to synthesize the data.

OBJECTIVES

To conduct a systematic review of the literature concerning the benefit of adding cyclosporin to oral corticosteroids in chronic stable adult asthmatics who were dependent on oral corticosteroids

METHODS

Criteria for considering studies for this review

Types of studies

All studies were required to be randomised double blind placebo controlled trials in stable steroid dependent adult asthmatics. All relevant studies were included.

Inclusion criteria

1. Cyclosporin used with either oral or parenteral administration.
2. Duration of therapy should have been sufficient to allow for any benefit accruing from cyclosporin to appear.
3. Initial therapy should include maximal inhaled corticosteroid and chronic use of oral prednisolone or another oral corticosteroid preparation. Minimum duration of prior therapy had to be at least three months.

Exclusion Criteria

1. Subjects who were not on chronic oral corticosteroids prior to trial.
2. Inadequate trial duration (<12 weeks).

Types of participants

Inclusion criteria

1. All trial patients diagnosed with "asthma" defined in operational terms.
2. Adults, arbitrarily defined as greater than 16 years old.

Exclusion Criteria

1. Current smokers.

Types of interventions

The addition of cyclosporin or placebo in a blinded randomised fashion.

Types of outcome measures

Study outcomes reported a wide range of measurements, including at least one of the following:

1. Pulmonary function testing (PEF, FEV1 & any others).
2. Symptoms.
3. Use of rescue medications (e.g. bronchodilators).
4. Frequency of asthma exacerbations.
5. Alterations in steroid dosage.

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group Module for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms:

'cyclosporin* OR ciclosporin* OR neoral OR sandimmum OR sangcya'

These searches are current as of September 2010.

Searching other resources

Bibliographies from these primary papers and from review articles were surveyed for additional citations & RCTs. Trial authors were contacted for more information.

Data collection and analysis

Selection of studies

The titles and abstracts were reviewed to identify all potential RCTs. Full text versions of these articles were obtained.
Inclusion of studies was decided by two reviewers who independently read the methods section of all identified papers and applied the stated criteria.

Data extraction and management

This was performed by one reviewer and a second reviewer checked the data extraction. Inter-rater reliability was assessed by simple agreement.

Other characteristics of trial validity;
(i) "Chronic" & "Stable"
(ii) Use of inhaled corticosteroids
(iii) Prior attempts at reduction in oral corticosteroid dose (tapering)

Assessment of risk of bias in included studies

Trials were scored according to the Cochrane assessment of allocation concealment as well as by the 0-5 point scale of Jadad by two reviewers acting independently.

Data synthesis

The planned comparison was of cyclosporin versus placebo.

Comparisons were performed for each outcome. Outcome data was entered into RevMan 4.1 for statistical analysis. Categorical outcomes were assessed as odds ratios (OR) and 95% confidence intervals. Continuous outcomes were analysed as effect sizes. Fixed effects models were used to obtain summary statistics for the overall efficacy of cyclosporin upon specific outcomes.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was tested for, and if found, a sensitivity analysis done on the basis of methodological quality. If heterogeneity still existed a sub-group comparison was made on the following basis:

A Size of study
B Optimal inhaled corticosteroid use
C Pre trial steroid tapering
D Disease severity

RESULTS

Description of studies

Results of the search

Literature searches identified six trials, three of which were randomised controlled trials fulfilling criteria for selection into systematic review (Alexander 1992; Lock 1996; Nizankowska 1995). With the exception of the trial published by Alexander attempts to contact the authors for more detailed information were unsuccessful. Study design, initial doses of oral and inhaled corticosteroids and reported outcomes varied between the trials. Alexander et al stated their intention to measure efficacy of cyclosporin rather than steroid sparing qualities and therefore no attempts to reduce the dose of steroid was made during this study. Update searches conducted in September 2008 and 2010 did not identify any additional studies.

Included studies

Three studies were identified, all of which were published as full articles. All studies were published in English language publications. The available trials were relatively small and of short duration. All patients had demonstrable reversibility of FEV1 following inhalation of beta-agonists (15 to 20% depending on the study). All trials excluded smokers and patients with significant co-morbidity.

Each trial will be described in detail:

Alexander 1992 studied 30 patients with a mean systemic corticosteroid dose of 8.5 mg a day received cyclosporin in a placebo controlled cross over study. The treatment period was 12 weeks and the mean cyclosporin levels was 152 ng/ml. This efficacy study showed significant improvements compared to placebo in lung function and exacerbations but no differences in symptom scores or rescue medication use (see results). Analysis of an 11 week run out period showed the mean morning PEFR remained significantly higher compared to baseline following cyclosporin treatment.

Nizankowska 1995 examined both the efficacy and possible steroid sparing effects of cyclosporin in 32 patients. These individuals were steroid dependent as demonstrated by failed attempts to taper systemic corticosteroid in the 6 months prior to study entry. The mean dose of prednisolone in this group of patients was 16 mg a

day. In this study the mean cyclosporin level was 120 ng/ml. No benefits were recorded for lung function in the efficacy treatment phase of 12 weeks although there were significant differences in symptom scores and rescue medication use in favour of the cyclosporin patients. During the steroid sparing phase (22 weeks) no significant differences were seen between the two groups for steroid reduction or exacerbation rates (see results). The authors concluded no benefits following the introduction of cyclosporin.

Lock 1996 studied the steroid sparing effects of cyclosporin using a placebo controlled parallel study design. Thirty nine patients were studied and all were established steroid dependent asthmatics with a mean daily prednisolone dose of 12 mg. Contrary to the reports of Nizankowska, this study showed significantly greater steroid reduction in cyclosporin treated patients of 25% compared to placebo for 'lowest dose' steroid during the 36 week treatment phase (i.e. not necessarily at the end of treatment periods). However over the whole duration of treatment there was no statistically significant difference between treatment groups despite the fact that the within group steroid reduction for cyclosporin was significant. Despite reductions in steroid treatment the cyclosporin patients showed significant increases in PEFR, although no change in any other parameter of lung function or symptom scores (see results). The mean cyclosporin level during this study was 144 ng/ml.

Risk of bias in included studies

Quality of trials

Trials were scored according to the Cochrane assessment of allocation concealment as follows;
A adequate concealment
B uncertain
C clearly inadequate

Trial quality was also scored according to the 0-5 point scale of Jadad and assessed by two reviewers acting independently.

Other characteristics of trial validity assessed were;

(i) "Chronic" & "Stable", assessed operationally in terms of duration of prior oral corticosteroid therapy & variation in dose during that period.

(ii) Use of inhaled corticosteroids. This was graded:
A. Optimal
B. Sub optimal
C. Not stated

(iii) Prior attempts at reduction in oral corticosteroid dose should have been unsuccessful in eliminating chronic use. A "run in" period on a steady dose of oral corticosteroid following an attempt at reduction of corticosteroid dose was identified as an important component of the trial design. Studies lacking this will be graded accordingly:
A. Steroid dose reduction attempted
B. No steroid dose reduction attempted
C. Not stated

The studies lacked sufficient detail regarding methods of randomisation and this was the reason why any of the trials failed to gain a Cochrane 'A' rating.

The overall ratings for the trials were; Alexander: B; Lock: B; Nizankowska: B.

Effects of interventions

Two of the three trials that were analysed were parallel group studies. Alexander et al reported data from a cross-over design trial. Nizankowska et al reported both efficacy and steroid sparing phases, Alexander et al studied efficacy measures of cyclosporin whilst Lock et al evaluated possible steroid sparing effects of the drug. These latter two trials used doses of cyclosporin of 5 mg/kg (achieving mean serum levels of 152 ng/ml and 144 ng/ml respectively). In contrast the patients randomised to cyclosporin in the Nizankowska et al study underwent dose titration to serum levels of 75-150 ng/ml.

A total of 106 patients were enrolled to these studies and data from 98 were available for analysis. Across the studies there were 10 withdrawals, although data from 2 were included in final analysis of cyclosporin effects (both in the study by Lock et al). Two patients were withdrawn due to unwanted effects during cyclosporin treatment, four due to uncontrollable asthma, one protocol violation, two patients moved away from the study centre and were lost to follow up and one death due to cardiac arrhythmia (Lock et al). All of the studies were of comparable size.

The trials were of varying duration. Alexander et al reported effects over 12 weeks of treatment, Lock et al over 36 weeks and Nizankowska et al over 12 weeks for the efficacy limb and 22 weeks for the steroid sparing phase of the study.

The patients in each of the trials showed only slight differences in terms of asthma severity. The characteristics of the patients for age and measures of lung function (FEV1 and FVC) were similar across the studies. All patients were non-smokers. The mean dose and duration of oral corticosteroid treatment is shown in Table 1.

Prior to randomisation the lowest dose of steroid that maintained each patient's asthma in a stable state was established (tapering) for all three studies.

The studies varied in their stipulated primary outcome measures. Alexander et al stated that morning /evening PEFR and exacerbation rates were the primary outcome whereas Lock et al measured the lowest steroid dose (maintained for 2 weeks) during treatment. For Nizankowska et al the primary outcome variables for each of the two phases were not clearly stipulated and a number of variables were presented. For phase one, measures of lung function, exacerbation rates and scores from patient held diary cards (symptoms, rescue medication use, PEFR) were expressed as outcome variables whereas in phase two, the percentage of the patient groups showing a 20% fall in steroid dose as well as actual changes in steroid dose were reported as outcomes.

A meta-analysis of the data was performed using the lowest dose of steroids achieved in the Lock and Nizankowska studies. There was a significant treatment effect (SMD -0.5; 95% CI -1.0,-0.04, Analysis 1.2). No significant heterogeneity was found.

No data concerning lung function and asthma control were presented in a form that could be extracted and subjected to meta-analysis. Alexander et al reported significant improvements of am/pm PEFR, FEV1, FVC and exacerbation rates for cyclosporin treated patients. No difference was seen between the groups for measures

of symptoms or rescue medication use. Likewise Lock et al showed significant improvements between groups for am PEFR, but no significant difference in FEV1, FVC or symptom scores. The efficacy limb of the Nizankowska study showed no difference in measures of lung function between the treatment groups. However there were improvements for symptom scores and rescue medication use in favour of the cyclosporin treated patients.

Side effects were common on cyclosporin. This information was expressed in various ways between the studies but where possible data were extracted and analysed. Modest but significant increases in diastolic blood pressure were found in patients treated with cyclosporin (SMD 0.8, 95% CI 0.3, 1.3). There were no significant changes in systolic blood pressure. Data from the Alexander trial could not be analysed in the meta-analysis although significant increases in blood pressure were noted in the cyclosporin group. The plasma creatinine also rose (SMD 0.9, 95% CI 0.4, 1.4). Measures glomerular filtration rate were impaired in the cyclosporin treated patients in all three trials but these changes were noted to be reversible on discontinuing the drug. Abnormalities of liver enzymes (alkaline phosphatase) were recorded in the Alexander and Lock studies. Nausea, vomiting, paraesthesia, and hypertrichosis were all documented amongst cyclosporin treated patients.

DISCUSSION

This review has studied three randomised controlled trials looking at the effects of cyclosporin amongst a group of steroid dependent asthmatics. The authors in each study conclude that this drug has either efficacy or steroid sparing qualities or both. The treatment effects vary between these trials and Nizankowska et al, unlike the authors of the other two trials, question the clinical meaning of their findings. The trials vary in methodology and have some limitations that influence the interpretation of the results of this review.

Oral corticosteroid dependent patients account for approximately 1% of the total with the asthma, but consume a disproportionate amount of available resources. They are at serious risk of debilitating side effects from chronic steroid dosing, notwithstanding the risk that severe chronic asthma poses to their health. It is important to improve the treatment for this group and this underpins the need for trials looking at 'add on' therapies using potent and potentially toxic immunosuppressive agents such as cyclosporin.

Given this clinical challenge it becomes obvious that there are two fundamental and separate outcomes to consider in the development of novel treatment strategies, namely efficacy and steroid sparing qualities. The recognition of these outcomes is important to the whole question of understanding trial design. Studies looking at efficacy should make no attempt to reduce the dose of steroids and measure improvement in terms of function and asthma control whereas steroid sparing trials examine dose of steroid needed to maintain clinical control. The primary outcome measure of trials therefore defines the type of trial. Extracting functional data from a steroid sparing trial to test efficacy or examining steroid doses in an efficacy trial may be misleading when combining the overall effects of 'add on' drugs. Alexander et al stipulated that their trial was designed to measure efficacy so made no attempt to reduce the steroid dose. The study reported by Nizankowska et al was carefully designed and had both steroid sparing and efficacy phases. This allowed data from this study to be used in the review to consider both characteristics of cyclosporin. Lock et al conducted a steroid sparing trial.

Efficacy of drugs used to treat asthma should be measured in terms of lung function (PEFR, FEV1, FVC etc) and markers of asthma control (symptom scores, exacerbation rates, quality of life scores etc). All of the reported studies in this review looked at markers of function and asthma control. With reference to markers of asthma control, no quality of life scores were done and only the study reported by Alexander et al included a marker of asthma control (exacerbations) amongst the primary outcome variables. All of the studies made measurements of parameters such as symptom scores and exacerbation rates although no actual data was presented in the study by Lock et al.

The second desirable characteristic of 'add on' treatments in this group of asthmatics relates to steroid sparing effects. A drug that shows efficacy is not necessarily a steroid sparing agent as well, so attempts should be made to demonstrate this quality separately from efficacy. Two of the trials reported in this review, Lock et al and Nizankowska et al, looked at the ability of cyclosporin to reduce the dose of oral corticosteroids.

Overall the trials were small with approximately thirty patients in each (although the trials were of similar size). No significant heterogeneity was identified for any outcome measure used in the meta-analysis. None of the trials included in the review presented power calculations (the study by Nizankowska et al did not stipulate primary outcome variables). Clearly this may be of importance given that Alexander et al presented non-significant results for measures of asthma control, and Nizankowska et al (efficacy limb) for measures of lung function, morning PEFR, and symptom scores. In the Lock study no data for the final dose of steroid at the end of the 36 week treatment period is given and is it assumed that this showed no significant differences between the groups. This result is potentially important in the context of the trial design and a type 2 statistical error cannot be excluded.

The duration of these studies was brief when considered in the context of chronic asthma and the assumptions made about mechanisms of action for disease modifying immunosuppression. The longest treatment period was 36 weeks (Lock et al). Efforts to show definitive effects for cyclosporin may be hindered by short treatment trial duration.

All of the trials stated that tapering of steroids during the run in to the study periods was done, hence minimising error arising from falsely positive benefits arising from excessive steroid doses amongst the study subjects. The trial reported by Alexander was a cross-over design with a 2 week wash-out period. The other two trials were both parallel group design. Given the results from the methotrexate review published by Davies et al (1998), it would seem that caution should be expressed about cross-over studies with short washout periods between treatment limbs. This study design may have an effect on results, favouring placebo. There were insufficient trials to assess the effects of parallel and cross-over designs on the estimated efficacy of cyclosporin. The trial results from Alexander et al did not report carry over and sequence effects.

The meta-analyses were limited by differences in the way data for steroid doses were expressed by Lock et al and Nizankowska et al - the two steroid sparing trial designs. In the former trial, the

lowest steroid dose maintained for two weeks during the treatment period was given as well as the total cumulative dose of steroid for the whole treatment period. No data for doses at the end of the dosing period were shown. In Nizankowska, a more usual presentation of the effects of treatment over the trial period were given. The difference in method of presenting these data required the calculation of a standardised mean rather than a weighted mean difference which would have expressed the steroid dose in mg/day.

Despite the methodological problems highlighted for these studies there were statistically significant effects of cyclosporin on steroid doses (SMD -0.5, 95% CI -1.0,-0.04). For Nizankowska 1995 this effect amounted to a mean reduction of 6.1 mg in the cyclosporin treated patients and 4.3 mg in the placebo treated patients. Estimates derived from the total cumulative steroid dose in Lock 1996 show an even smaller incremental reduction in the daily steroid dose when compared to placebo. The question remains as to whether these effects are clinically important. Clinically useful effects of cyclosporin on lung function and asthma control might favour the drug without necessarily requiring a steroid sparing effect. In fact it was not possible to pool spirometric data, symptom scores or rescue medication in meta-analyses so no overall effect could be calculated. The Nizankowska study showed no significant benefits for FEV1, FVC, PEFR (in fact post-bronchodilator PEFR favoured placebo) although there were small but significant benefits in favour of cyclosporin for rescue medication use. The Alexander trial (Alexander 1992) showed significant improvements for morning PEFR (approximately 45 l/min), FEV1, and FVC. Overall the results are mixed and do not provide strong evidence of efficacy or steroid sparing effects.

None of the trials examined possible mechanisms of action for cyclosporin such as measures of airways inflammation. Cyclosporin is known to have inhibitory effects on a number of inflammatory pathways inclusive of lymphocytic expression of a cytokines that may be relevant to the immuno pathology of asthma. Clearly an interpretation of the results of the individual studies (and indeed the meta-analysis findings) as indicative of a real positive effect of the drug would be more tenable if mechanistic data supporting the clinical findings had been available.

With reference to safety, the comparisons employed by this review show significant untoward effects of cyclosporin on diastolic blood pressure and plasma creatinine and a worsening of glomerular filtration rate that reversed on discontinuation of the treatment.

In summary the three trials included in this review amount to a relatively small body of evidence. There are flaws in each that weaken any interpretation of the results reported. Nevertheless the data show that addition of cyclosporin did produce a modest reduction in steroid dose and small improvements in lung function. The clinical relevance of these changes, even if the assumption is made that they represent real effects of the drug alone, is debatable. From the perspective of safety there are definite changes in blood pressure and renal function that militate against the use of cyclosporin. The potential benefits in terms of reduced steroid risk cannot be quantified but it seems unlikely that significant clinical gain would be forthcoming.

AUTHORS' CONCLUSIONS

Implications for practice

Cyclosporin produces only a small reduction in daily oral corticosteroid dose and a small improvement in spirometry. This should be set against a rise in diastolic blood pressure and plasma creatinine. The available evidence does not support its use on a routine basis in the treatment of steroid dependent asthma. If prescribed at all, this agent should be used only by experienced physicians with a specific expertise in this field.

Implications for research

Further randomised controlled trials with sufficient power to conclusively evaluate cyclosporin in terms of efficacy and steroid sparing effects (i.e. separate trial designs) are required to clarify whether the small effects demonstrated by this meta-analysis represent clinically significant changes. It will then be possible to assess whether benefits, if any, can be applied to clinical practice.

ACKNOWLEDGEMENTS

I would like to express thanks to the members of the Airways Group in particular Steve Milan, Toby Lasserson, Anna Bara and Karen Blackhall who helped in the acquisition and translation of a number of articles in the preparation of this review. We would like to thank Prof Barry Kay for corresponding with us regarding his study.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alexander 1992

Methods	Randomised, double-blind, crossover. 4 week run-in, 12 week treatment periods, with 2 weeks washout between treatments. Analysis over last 4 weeks of each treatment period only.

Alexander 1992 *(Continued)*

Participants	33 patients were enrolled, 13 men 20 women. 30 patients received both CyA and placebo, 26 patients completed the full protocol. Age range 21-64, mean 49y. Non-smokers. Mean (range) daily initial OCS 8.5mg (5-20), Mean (SE) daily ICS 1665 (90) mcg Mean (SE); PEFR 239(19) L/min FEV1 1.73(O.14) L VC 3.09(0.21) L
Interventions	Patients randomised to receive CyA 5mg/kg or placebo for 12 weeks prior to cross-over after 2 week washout. Primary outcome variables were changes in mean morning and evening PEFR and frequency of asthma exacerbations.
Outcomes	CyA resulted in a mean increase above placebo of 12% in morning PEFR (p<0.004) and 17.6% for FEV1(p<0.001). The frequency of exacerbations requiring an increase in the dose of OCS was reduced by 48% in patients on CyA compared to placebo (p<0.02). Mean concentration CyA 152 micrograms/mL.
Notes	Data from last 4 weeks analysed only. Inadequate information regarding allocation concealment. Efficacy trial , no attempts made to reduce steroid dose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Described as randomised; other information not available

Lock 1996

Methods	Randomised, double-blind, parallel group. 4 week run-in, 36 week treatment, 8 week double blind placebo phase and 4 week run-out.
Participants	39 patients enrolled, data from 36 was used in the assessment of steroid dose reduction. Mean age 50y (26-66) 19 men, 17 women Non-smokers Mean (range) daily OCS; CyA, 11mg (5-20):Placebo 12mg (5-22.5). Mean daily ICS 2.1mg. Mean (SE), & % predicted FEV1;CyA 1.69(0.15) 63.3%: Placebo 2.02L(0.16) 68.7% Mean(SE) & % predicted FVC; CyA 2.89L(0.19) 80%:Placebo 3.35L(0.26) 83%.
Interventions	Pre-trial tapering OCS. Randomised to CyA 5mg/kg or placebo. Reviewed every 14d, prednisolone dosage reduced if asthma stable by between 1.25 and 5mg per week as per pre-set protocol. Primary outcome variable - lowest dose of steroid (maintained for two weeks) during treatment phase.
Outcomes	Median reduction prednisolone expressed as a % of baseline; CyA 62%, placebo 25%. CyA allowed a 25% reduction in excess of that seen in placebo (p<0.043). Total dose prednisolone during treatment; CyA 2484mg;placebo 3592mg (p=0.049). Fewer exacerbations in CyA treated patients (2.69/patient cf 3.55/patient) p= NS. Mean morning PEFR increased significantly in CyA patients, no change placebo (p=0.026 between groups). Neither treatment changed mean FEV1,FVC,PEFR variability, or beta-agonist reversibility.

Lock 1996 *(Continued)*

	Mean CyA level 144ng/mL.
Notes	Paper analysed best 2 weeks. Inadequate information regarding allocation concealment. Authors did not respond to correspondence seeking clarification. No end of treatment doses of prednisolone given. Initial ICS dose not stated. Results given as SEM converted to SD for analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Described as randomised; other information not available

Nizankowska 1995

Methods	Randomised, double blind parallel group. 12 weeks baseline, 12 weeks efficacy period, 12 weeks steroid tapering period, 8 weeks run-out.
Participants	34 patients were enrolled, 32 completed the protocol. 7 men, 27 women. Non-smokers Mean (range) age; CyA 42y (27-55):placebo 43y (27-58). Mean(SD) OCS ; CyA 15.9mg (6.9): placebo 16.5mg (7.5). All patients treated with 1.6mg ICS daily. Mean (SD) am PEFR; CyA, 233L/min (69): placebo, 235L/min (81). Mean (SD) FEV1; CyA 2.1L (0.8): placebo 1.9L (0.8). Mean (SD) FVC; CyA 2.9L (1.0): placebo 2.6L (0.9).
Interventions	Patients randomised to CyA or placebo. No details of pre-trial tapering given, but lowest dose of steroid maintaining stable state of asthma stipulated. CyA dose titrated to a level of 75-150 ng/mL. Assessed every 2 weeks during efficacy phase. Attempts to reduce prednisolone dose 10-15% every 4 weeks as per pre-set protocol. Outcomes; Phase one, measures of lung function: Phase two; % reduction in steroid dose.
Outcomes	Phase 1, efficacy; No differences between groups for am PEFR, pm PEFR, FEV1, FVC, FER, reversibility, global asthma scores. However there were significant benefits in favour of CyA for day and night consumption of fenoterol and day and night symptom scores from the patient diary cards. Phase 2, tapering; Reductions in dose were possible in both groups. CyA, 15.9mg to 9.8mg ($p<0.001$): placebo 16.5mg to12.2mg ($p<0.01$). No significant difference between groups. No differences in number or duration of exacerbations between groups during phase 2.
Notes	Inadequate information on allocation concealment. Authors did not respond to correspondence seeking clarification.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Described as randomised; other information not available

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

Study	Reason for exclusion
Kay 2003	Non-randomised study.
Khan 2000	Participants not treated with oral steroids at baseline
Matusiewicz 1992	Non 'randomised controlled trial'. 15 patients receiving cyclosporin showed improvements in lung function and reduction in doses of prednisolone.
Matusiewicz 1997	No placebo control.
Mungan 1995	Non 'randomised controlled trial'. 12 asthmatics treated with CyA for 3 months. No control group. Significant reductions in steroid dose and 34% improvement in FEV1.
Szceklik 1991	Non 'randomised controlled trial' . 12 asthmatics treated with CyA for 9 months. No control group. 6 of the patients responded to treatment.

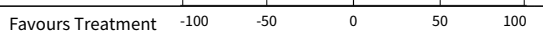
DATA AND ANALYSES

Comparison 1. Cyclosporin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEFR	1	60	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-18.38, 10.38]
2 Dose steroids	2	68	Std. Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.02, -0.04]
3 Blood pressure- systolic	2	73	Std. Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.16, 0.76]
4 Blood pressure - diastolic	2	73	Std. Mean Difference (IV, Fixed, 95% CI)	0.80 [0.32, 1.28]
5 Creatinine	2	73	Std. Mean Difference (IV, Fixed, 95% CI)	0.90 [0.41, 1.39]
6 Liver enzymes	1	39	Mean Difference (IV, Fixed, 95% CI)	50.78 [19.49, 82.07]

Analysis 1.1. Comparison 1 Cyclosporin vs placebo, Outcome 1 PEFR.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Alexander 1992	30	-17.7 (31.7)	30	-13.7 (24.7)		100%	-4[-18.38,10.38]
Total ***	**30**		**30**			**100%**	**-4[-18.38,10.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.59)							

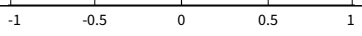


Analysis 1.2. Comparison 1 Cyclosporin vs placebo, Outcome 2 Dose steroids.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Lock 1996	16	2484 (1300)	20	3529 (1788)		51.93%	-0.64[-1.32,0.03]
Nizankowska 1995	17	-6.1 (4.1)	15	-4.3 (4.6)		48.07%	-0.41[-1.11,0.29]
Total ***	**33**		**35**			**100%**	**-0.53[-1.02,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%							
Test for overall effect: Z=2.13(P=0.03)							

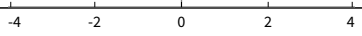
Analysis 1.3. Comparison 1 Cyclosporin vs placebo, Outcome 3 Blood pressure- systolic.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Lock 1996	19	1.9 (16.6)	20	-1.8 (10)		53.57%	0.26[-0.37,0.89]
Nizankowska 1995	17	133 (15.3)	17	128 (13.5)		46.43%	0.34[-0.34,1.02]
Total ***	**36**		**37**			**100%**	**0.3[-0.16,0.76]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.87); I^2=0%							
Test for overall effect: Z=1.27(P=0.21)							



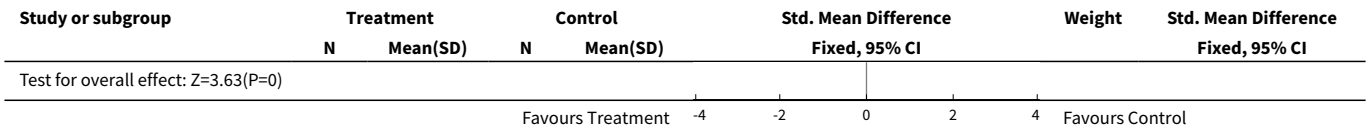
Analysis 1.4. Comparison 1 Cyclosporin vs placebo, Outcome 4 Blood pressure - diastolic.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Lock 1996	19	5.5 (6.6)	20	-0.1 (0.3)		49.67%	1.17[0.49,1.86]
Nizankowska 1995	17	85 (10)	17	81 (8.2)		50.33%	0.43[-0.25,1.11]
Total ***	**36**		**37**			**100%**	**0.8[0.32,1.28]**
Heterogeneity: Tau^2=0; Chi^2=2.3, df=1(P=0.13); I^2=56.49%							
Test for overall effect: Z=3.24(P=0)							

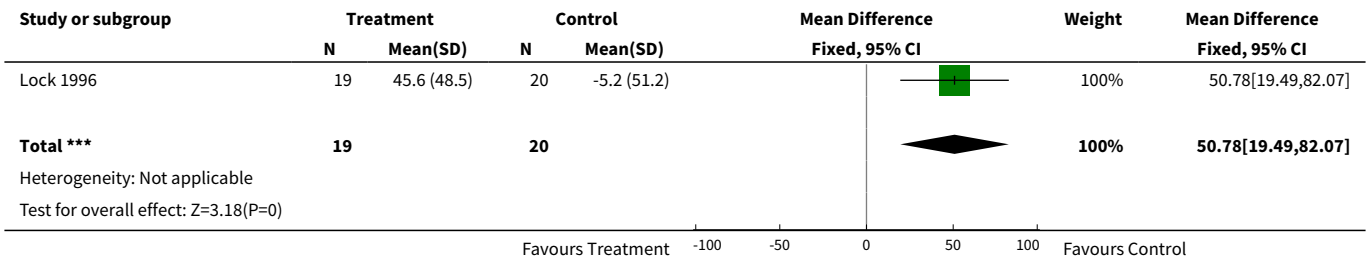


Analysis 1.5. Comparison 1 Cyclosporin vs placebo, Outcome 5 Creatinine.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Lock 1996	19	8.3 (10.9)	20	-2.7 (7.5)		50.6%	1.15[0.47,1.83]
Nizankowska 1995	17	99.4 (16.3)	17	90.8 (8.8)		49.4%	0.64[-0.05,1.33]
Total ***	**36**		**37**			**100%**	**0.9[0.41,1.39]**
Heterogeneity: Tau^2=0; Chi^2=1.06, df=1(P=0.3); I^2=5.41%							



Analysis 1.6. Comparison 1 Cyclosporin vs placebo, Outcome 6 Liver enzymes.



ADDITIONAL TABLES

Table 1. Pre treatment daily oral steroid dose mg/day (range)

Trial	Cyclosporin treated	Placebo treated	Years (range)
Alexander 1992	8.5 (5 20)	8.5 (5-20)	9.3 (0.3 - 25)
Lock 1996	11 (5-20)	12 (5 - 22.5)	12 (1-37)
Nizankowska	15.9 (10 - 25)	16.5 (5 - 27.5)	8 (2.5 - 22)

WHAT'S NEW

Date	Event	Description
3 September 2010	New search has been performed	Literature search re-run; no new studies found

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 1, 2001

Date	Event	Description
26 September 2008	New search has been performed	Literature search re-run; no new studies found
23 July 2008	Amended	Converted to new review format.

Date	Event	Description
1 August 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Evans DJ - Inclusion/exclusion criteria, quality assessment, data extraction/entry, data analysis, preparation of text, interpretation and conclusions
Cullinan P - Inclusion/exclusion criteria, quality assessment, data extraction/entry, data analysis, preparation of text, interpretation and conclusions
Geddes DM - Intellectual direction/supervision, interpretation and conclusion
Jones PW - Intellectual direction/supervision, interpretation and conclusion

DECLARATIONS OF INTEREST

Prof E. Haydn Walters has acted as a consultant to Norvartis who manufacture Neoral a form of cyclosporin.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- NHS Executive, South East, UK.

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Asthma [*drug therapy]; Cyclosporine [*administration & dosage] [adverse effects]; Immunosuppressive Agents [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Steroids [administration & dosage]

MeSH check words

Humans