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Troleandomycin as an oral corticosteroid sparing agent in stable asthma (Review)

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Troleandomycin as an oral corticosteroid sparing agent in stable asthma.
Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002987.
DOI: 10.1002/14651858.CD002987.

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[Intervention Review]

Troleandomycin 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. Troleandomycin as an oral corticosteroid sparing agent in stable asthma. *Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No.: CD002987. DOI: 10.1002/14651858.CD002987.

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. Troleandomycin is a compound that is established as an effective antibiotic but may also have non-antibacterial actions that may be useful in the treatment of asthma.

Objectives

The objective of this review was to assess the effects of adding troleandomycin 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. Searches are current as of September 2010.

Selection criteria

Randomised trials looking at the addition of troleandomycin 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 112 patients were recruited into these studies. Data from 90 patients were analysed. There was no treatment effect for troleandomycin in terms of steroid dose reduction (SMD -0.29, 95% CI -0.75, 0.17). For measures of lung function a meta-analysis of data derived from two of the included studies showed no benefits for added troleandomycin (SMD 0.06 95% CI -0.8, 0.9).

Authors' conclusions

There is insufficient evidence to support the use of troleandomycin in the treatment of steroid dependent asthma.

PLAIN LANGUAGE SUMMARY

Troleandomycin as an oral corticosteroid sparing agent in stable asthma

Troleandomycin is a macrolide antibiotic with established effects in the treatment of infections. It alters the breakdown of corticosteroid drugs, so may be of benefit in asthma. This review found three small studies, that provide no evidence to justify the use of this drug in asthma.

BACKGROUND

The recognition that asthma is a consequence of airway 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, neuro psychiatric 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, cyclosporin A, and troleandomycin. The concept that these drugs may be of benefit in asthma has arisen from studies showing benefits in other inflammatory conditions such as rheumatoid arthritis and psoriasis. To date only methotrexate in asthma has been reviewed. Troleandomycin is a macrolide antibiotic with established effects in the treatment of infections. Its most likely mechanism of action relates to the inhibition of the clearance of methylprednisolone. However there is some in vitro work showing reductions in neutrophil chemotaxis, inhibitory effects on mitogen-stimulated lymphocytes, reductions in basophil histamine release, and airway mucous secretion. Overall however the evidence would support steroid related actions rather than direct immunomodulatory effects.

This conclusion arises from the finding that patients taking troleandomycin frequently manifest Cushingoid features in excess of that expected for the doses of steroid given, adding further weight to the arguments forwarded concerning its mode of action. In addition troleandomycin inhibits the metabolism of theophylline and this may in part explain the gastrointestinal upset it causes.

The use of troleandomycin 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 it 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 troleandomycin to oral corticosteroids in chronic stable asthmatics who were dependent on oral corticosteroids

METHODS

Criteria for considering studies for this review

Types of studies

All studies were randomised double blind controlled trials in stable steroid dependent asthmatics. All relevant studies were included.

Inclusion criteria

1. Troleandomycin treatment.
2. Duration of therapy should have been sufficient to allow for any benefit accruing from troleandomycin to appear.
3. Initial therapy included chronic use of oral prednisolone or another oral corticosteroid preparation. Minimum duration of prior therapy with oral corticosteroids was at least three months.

Exclusion Criteria

1. Inadequate duration of trial (less than 6 weeks)
2. Subjects who were not on chronic oral corticosteroids prior to trial.

Types of participants

Inclusion criteria

1. All trial patients were diagnosed with "asthma" defined in operational terms.

Exclusion Criteria

1. Patients who were current smokers

Types of interventions

The addition of troleandomycin 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. Quality of Life Scores.
6. Changes in steroid dosage.
7. Side effects & adverse effects.

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:

'troleandomycin OR triacetyloleandomycin OR oleandomycin OR tao OR evramycin OR evramicina OR cyclamycin OR "crl 613" OR aovine'

These searches are current as of September 2010.

Other sources

Bibliographies from these primary papers and from review articles were surveyed for additional citations & RCTs. Trial authors were contacted for more information. Studies in languages other than English were eligible for inclusion.

Data collection and analysis

Selection of trials

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.

Quality of trials

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 extraction

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).

Statistical Considerations

The planned comparison was of troleandomycin 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 troleandomycin upon specific outcomes.

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

RESULTS

Description of studies

Three studies were identified, all of which were published as full articles. All studies were published since 1990 in English language journals. They were all parallel group studies and were all carried out in steroid dependent subjects. They were all relatively small and mainly of short duration. All these patients had demonstrable reversibility of FEV1. All trials excluded patients with significant co-morbidity. None of the trials included smokers. All patients in these studies were maximally treated with inhaled bronchodilators and oral theophylline. Patients were maintained on inhaled steroids with the exception of the study reported by Nelson et al (Nelson 1993) where they were excluded. The initial dose of troleandomycin was 250 mg daily in all studies. Update searches conducted in September 2008 and 2010 did not identify any additional trials.

A detailed description of each study follows:

Ball 1990 studied 15 children, between 8 and 18 years, over a 2 week period. Study subjects were randomised to receive troleandomycin 250 mg daily (TAO) and methylprednisolone (MP), placebo with MP, or TAO with prednisolone in parallel groups. For patients switched to MP, the dose was calculated as 80% of the pre-randomisation prednisolone dose. The group consisted of 9 boys and 6 girls. The mean age was 13.5 years. All patients had been steroid dependent for a minimum of 3 years and had been subjected to steroid tapering prior to randomisation. Patients were assessed daily during the treatment period.

The authors found that all patients were able to tolerate at least a 50% reduction in the dose of their steroids. This change was not associated with any change in lung function or worsening in markers of asthma control. Limited long term follow up confirmed the TAO-MP group showed the most consistent stability in asthma control. Measures of airway responsiveness (AR) showed improvements in 4/5 patients in the TAO/MP group, 2/5 in the TAO/prednisolone group and none of the MP/placebo group. Differences between groups did not reach significance. No drug related adverse events or abnormalities of liver function were reported for TAO. One patient (MP/placebo) was noted to have raised intra-occular pressure at the beginning of treatment - this settled during the treatment phase with steroid reductions, and another developed acute psychosis (TAO/prednisolone). Both of these may have been related to steroid treatment. Pharmacokinetic studies showed reduction in MP clearance times in the patients on TAO/MP.

In conclusion the authors suggested that low dose TAO had beneficial steroid sparing effects in children that were not totally attributable to inhibition of MP clearance given the improvements seen amongst the TAO/prednisolone patients. They reported a protective effect of TAO against airway challenge with methacholine.

Kamada 1993: 18 children (11 boys), 6-17 years, completed the protocol. Patients were screened and threshold (i.e. lowest) doses of steroids were identified. Individuals were randomised to receive TAO/MP, TAO/prednisolone or MP/placebo. The dose of TAO was 250 mg daily. The treatment period was 12 weeks. Patients were monitored on the ward for the first 2 weeks of the study, thereafter weekly contact was maintained.

The maximum tolerated dose reductions were significant for each treatment group (80% TAO/MP, 55% TAO/prednisolone, 44% MP/placebo). There were significant differences between the TAO/MP group and the MP/placebo group. Similarly there were reductions in the requirements for added prednisolone treatment of exacerbations, the greatest effect seen in the TAO/MP patients although these changes did not reach significance.

There were no significant changes in lung function in the TAO/MP patients amongst whom there were less reported symptoms (p = 0.025). Worsened lung function was reported for the TAO/prednisolone treated patients. For AR there were reductions in the PC20 Methacholine in the TAO/MP (p = 0.011) and MP/placebo groups, whereas slight protection afforded by TAO/prednisolone. 2 patients experienced abnormalities of liver function on TAO.

The authors conclude that TAO is safe and is a reasonable option in the treatment of steroid-dependent asthma. They do not hypothesise about the relative contributions to these benefits with respect to direct effects and those mediated via steroid metabolism.

Nelson 1993: 57 patients (19 men), aged 21 - 75 years, completed the trial. Steroid tapering was undertaken prior to study entry and patients were randomised to receive TAO/MP or MP/placebo. The dose of TAO was 250 mg and the trial ran for one year (double-blind phase) with a single blind period during a second year for some of the study subjects.
29/30 patients receiving TAO/MP and 23/27 on MP/placebo managed to reduce steroids to an alternating day regime. The mean daily steroid dose for TAO/MP was 6.3 mg/day and for MP/placebo, 10.4 mg/day (p = 0.03). Control of asthma was maintained and similar in both groups. No differences were seen for steroid side effects between the two groups.

The authors conclude that the benefits seen in the TAO group were accountable to its effects on MP metabolism alone.

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) Concomitant medication.

All the subjects in these trials were maintained on theophylline and inhaled bronchodilators.

(ii) Use of inhaled corticosteroids.

This should be kept constant, unless the dose given was used as an outcome in the trial

In the Nelson 1993 study none of the subjects remained on inhaled steroids during the treatment phases and in the Ball 1990 study the use of inhaled steroids was variable. All the patients in the trial reported by Kamada 1993 et al were taking inhaled steroids.

(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.

Attempts to taper steroid doses before the treatment periods were stated explicitly only in Kamada 1993 et al. Nelson 1993 et al refer to tapering 'in a way consistent with good asthma control'. In fact this report states that at randomisation some of the patients were receiving higher doses of steroid than previously so as to ensure good control at the start of the study. No tapering was done in the trial reported by Ball 1990 et al. Criteria for steroid dependency was similar in the trials reported by Nelson 1993 et al and Ball 1990 et al, approximately 30 mg a day, although this parallel is difficult to draw given that the patients in the latter study were children. The patients reported in each of the treatment groups in the Kamada 1993 study had baseline doses of 21 mg, 24 mg, 34 mg a day. The duration of previous steroid therapy was not explicitly stated by Nelson 1993 et al although their patients were required to have been taking steroids for a minimum of 3 months. The patients in the study reported by Ball 1990 had been medicated with steroids over longer periods ranging from 6 months to 13 years. The three treatment groups in the Kamada 1993 trial had previously taken steroids for 2.5 years (TAO/MP), 4.7 years (TAO/prednisolone) and 5 years (MP/placebo) respectively.

Effects of interventions

The literature searches identified twelve trials of which 3 fulfilled criteria for selection into the review. Attempts to contact the authors for information were made and we are grateful to Drs Kamada and Bruchmeier (Nelson et al) for supplying further data.

Initially a total of 112 patients were enrolled and data was collected from 90 patients across the three trials reviewed. Of these 58 individuals completed the various protocols. The majority of the patients were included in the study by Nelson et al (75 patients enrolled).The trials were of varying duration; 2 weeks (Ball 1990), 12 weeks (Kamada 1993), and up to 24 months (Nelson 1993).

The various study groups were all diagnosed as asthmatic with no other pulmonary co-morbidity but no details of pre-trial lung function were given in any of the studies, with the exception of the patients reported by Ball 1990 et al whose subjects had a mean FEV1 of 83% at baseline.

The primary outcome variable in all trials was a reduction in the dose of steroids although this was not explicitly stated in any of the trials. Steroid data were expressed as both absolute doses for each patient as well as percentage reduction by Ball 1990 et al. Kamada 1993 showed the baseline and 12 week data for treatment groups. Nelson 1993 et al expressed results in terms of methylprednisolone dosage as well as reporting outcomes such as exacerbation rates, hospital visits and admissions for asthma. Individual patient data was used in this instance following receipt of the raw data from the authors. Overall there was no demonstrable benefit for the addition of TAO to methylprednisolone in terms of steroid dose reduction (SMD -0.29 95% CI -0.75, 0.17). No analysis was done comparing the effects of TAO and prednisolone since the studies were not specifically designed to address this and there were insufficient data for meta-analysis.

Meta-analysis of measures of spirometry derived from the data presented by Ball 1990 et al and Kamada 1993 et al shows no significant treatment effects of added TAO (SMD 0.06, 95% CI -0.8, 0.9). No change in pre-bronchodilator FEV1 was seen at the end of the first treatment year in the study by Nelson 1993 et al and no data for the second year are shown. In this trial no

differences between the groups for asthma control, exacerbations or hospital requirements were found although no specific data were presented. No differences were seen for exacerbations in the studies of Ball 1990 et al and Kamada 1993 et al. In the trial reported by Kamada 1993 et al symptom scores were not significantly reduced in the patients randomised to TAO-methylprednisolone.

For measures of bronchial reactivity the results in the three trials were mixed. Few of the study subjects in the trial by Nelson 1993 et al were able to undergo this test (11 on placebo, 13 on TAO). There were insignificant reductions in airways responsiveness in both groups and a trend towards greater improvements in the TAO patients (p = 0.08). Ball 1990 et al showed non significant improvements in airway responsiveness in the methylprednisolone-TAO patients and no changes in the prednisolone-TAO or methylprednisolone groups. In fact Kamada 1993 et al showed significant increases in airway responsiveness in the methylprednisolone -TAO group with non-significant changes in the other two treatment groups.

There were no withdrawals from treatment in the studies reported by Ball 1990 et al and one from the study by Kamada 1993 et al. 18 patients (7 TAO, 11 placebo) withdrew from the study reported by Nelson 1993 during the first year and a further 32 withdrew during the second year of double blind treatment. Reasons for exiting the study are not given although the authors found no significant differences between the withdrawing patients and the trial survivors for markers of asthma control in either placebo or TAO treatment. They conclude that the withdrawals were not due to treatment failures. No details concerning liver function were given in this paper. Two patients had clinically important abnormalities of liver enzymes in the study by Kamada 1993 et al and one of these was withdrawn from the study, the other resolved spontaneously. Liver function remained normal in all the subjects studied by Ball 1990 et al.

No theophylline toxicity was reported in any of the studies but levels required careful monitoring throughout. A 30% reduction in dose of theophylline was required in five patients studied by Ball 1990 et al.

The question as to whether the benefits measured in terms of steroid dose requirements was solely attributable to effects on methylprednisolone metabolism rather than any other effects of TAO was addressed by Nelson 1993 et al and Kamada 1993 et al. Ball 1990 et al measured methylprednisolone clearance rates and showed a 62% reduction on TAO but did not present any data on steroid side effects amongst the TAO responders. Nelson 1993 et al showed untoward and significant changes in bone density, lipids and fasting blood glucose in patients randomised to TAO-methylprednisolone despite lower doses of methylprednisolone indicating effects via steroid metabolism alone. Over the 12 weeks of treatment in the study by Kamada 1993 et al no objective features consistent with increased steroid effects (blood pressure, weight, bone densitometry etc) were measured in any of the treatment groups although two individuals in the TAO-methylprednisolone group developed marked Cushingoid features (vertebral collapse and striae respectively).

No significant heterogeneity was identified amongst the data analysed by meta-analysis.

DISCUSSION

The result from the meta-analysis of these three studies for steroid doses shows a trend in favour of TAO but no significant effects for TAO in terms of steroid sparing qualities (SMD -0.29 95% CI -0.75, 0.17). At first sight this may seem a surprising result since TAO might be expected to reduce steroid doses through it's effects on methylprednisolone clearance, notwithstanding any other beneficial asthma effects. However, this pre-supposes a steep dose=response effect for oral corticosteroids in asthma, which has not been shown. Nelson 1993 et al found a significant effect for steroid dose in favour of the TAO group at one year but the baseline doses for placebo and TAO were significantly different making comparisons of dose differences at time points thereafter difficult. Analysis of changes in dose between baseline and one year for individual patients (kindly supplied by the authors and used in the meta-analysis) shows no significant treatment effects between groups.

There are some important differences between these studies that are worthy of mention in the interpretation of this review. The most important of these relates to the study subjects. Two of the trials examined the effects of TAO in groups of steroid dependent children. Very little data that could be used to define the severity of the subjects is given in any of the trials. There are inconsistencies in the use of inhaled steroids across these three trials. This is an important deficit in the usefulness of the review given the importance of inhaled corticosteroids as 'steroid sparing agents'. The use of theophylline is an important and potential confounding variable. TAO interferes with theophylline clearance and therefore benefits in asthma control may arise from increases in the effective serum levels of this drug. In fact all three studies titrated doses of theophylline and as far as can be surmised this factor was appropriately controlled. The studies by Ball 1990 et al and Kamada 1993 et al were small and of short duration. Efforts to show conclusive effects for TAO may be hindered by short treatment trial duration. Nelson 1993 et al report a larger group of adults over one year with a smaller number of patients going on to complete a second study year. The results from both the studies by Ball 1990 et al and Nelson 1993 et al need to be interpreted with caution as there was no formal tapering of steroids during run-in to the treatment periods. It is difficult to draw conclusions from a review of such diverse research methodology.

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). Nelson 1993 et al made no attempt to demonstrate efficacy. Their study was designed to look at steroid doses and markers of steroid side effects with a view to demonstrating mechanisms of action for TAO. As predicted by the authors, there were no significant differences between the groups for these parameters. Neither of the other two studies showed significant changes in lung function or markers of asthma control. There were trends towards improvements in airway responsiveness in these latter studies although no mechanisms other than steroid related benefits have been proposed.

None of the reports calculated the power of the study. Type 2 statistical errors cannot be excluded in these instances and this may be of particular importance to the measures of airways responsiveness made by Ball 1990 and Kamada 1993.

All three studies looked at the issue of steroid related side effects in an attempt to demonstrate a mechanism for TAO. Efforts to find non-steroid related asthma benefits were done by making measures of airways reactivity to methacholine although no other end points such as bronchial biopsy were done to elucidate mechanisms. Clearly techniques such as this would have been difficult in children notwithstanding the severity of the patients across all three studies. The studies reported by Ball 1990 et al and Kamada 1993 et al were small and too brief to add meaningful data to the understanding of how TAO might work. Nevertheless Ball 1990 et al confirmed significant reductions in the clearance of methylprednisolone (not seen for prednisolone) in keeping with the argument that the drug works in this way. Nelson 1993 et al were able to show significant and untoward effects on steroid levels as manifest by changes in fasting blood glucose, lipids and bone densitometry. They conclude that TAO mediated it's modest effects through the reduction in methylprednisolone clearance. These effects are not seen for prednisolone and the consensus view from other publications would support this.

With reference to safety issues unrelated to steroid side effects, there was also shortage of data for entry into meta-analysis. Interestingly the important side effect of TAO, namely abnormalities of liver function did not emerge as a major problem from the two studies reporting this data. Two patients in the study by Kamada 1993 et al showed abnormalities, but no problems were presented in the trial by Ball 1990 et al.

In summary the three trials included in this review amount to a relatively small body of evidence. There are flaws in each study and differences between the trials that further weaken the meaning of the combined results. Overall, the data show no significant effect on oral steroid dose. From the perspective of safety, whilst there are established serious side effects of this treatment, this review has not demonstrated significant untoward changes in parameters such as liver function. Nevertheless there are changes that suggest augmentation of steroid effects inclusive of side effects. This is endorsed by pharmacokinetic data presented in one of the studies. Under these circumstances the potential benefits in terms of measured reduced steroid doses are clinically insignificant and the available evidence does not support the use of TAO as a steroid sparing agent in asthma.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence available does not support the use of TAO as a steroid sparing agent in the treatment of asthma.

Implications for research

Further randomised controlled trials with sufficient power to conclusively evaluate TAO whether the beneficial effects that are not attributable to potentiation of steroid actions exist. These trials should be undertaken amongst adult patients who are optimally managed on inhaled steroids following careful tapering during run-in.

ACKNOWLEDGEMENTS

I would like to express thanks to the members of the Airways Group in particular Steve Milan, Toby Lasserson, Anna Bara, Karen Blackhall and Susan Hansen who helped in the acquisition and translation of a number of articles in the preparation of this review.

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Kamada 1993 *{published data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ball 1990

Methods	Randomised, double blind, placebo controlled, parallel groups trial. Threshold doses of prednisolone identified during pre-trial screening. Two week treatment period.
Participants	18 patients enrolled, 15 completed protocol from whom the data was analysed. No demographic differences between groups stated. 9 male, 6 female. Mean (SD) age, 13.5y (2.58). Maintained on ICS (no dose details) and theophylline, inhaled bronchodilators. Mean(SD) dose prednisolone, 31mg (17.8).

Ball 1990 *(Continued)*

	Mean (SD) % predicted FEV1, 83% (20.4).
Interventions	Randomised to receive TAO/MP, MP/placebo TAO/pred. TAO 250mg daily. Primary outcomes not stipulated. Assessed daily. Steroids tapered from day 3 to 14. Spirometry, methacholine challenge and glucocorticoid kinetic studies done at day baseline and day 14.
Outcomes	All patients reduced steroid dose by at least 50%. No changes in lung function or increase in reported symptoms in any group. AR improved in TAO/MP and TAO/pred (NS). Long term follow up showed enduring benefits in patients maintained on TAO/MP. TAO well tolerated.
Notes	Inadequate information regarding allocation concealment. Authors did not respond to enquiries seeking clarification. Insufficient data available to calculate SD for asthma control or exacerbations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kamada 1993

Methods	Randomised, double blind, placebo controlled, parallel group trial. Minimum dose of steroids identified during screening period. 1 week run-in, 12 week treatment period.
Participants	19 enrolled, 18 completed protocol from whom data was analysed. TAO/MP group significantly taller than MP/placebo group, otherwise no demographic differences between groups. 11 male, 7 female. Age range 6-17y. All patients treated ICS, theophylline and inhaled bronchodilators. No dose details for ICS. Mean (SE) daily OCS (mg); TAO/MP 34.2 (9.6); TAO/pred 21.3 (3.1); MP/placebo 23.5 (5.7). Mean (SE) PEFR (L/min); TAO/MP 368 (39); TAO/pred 313 (41); MP/placebo 313 (36).
Interventions	Randomised to receive TAO/MP, TAO/pred, or MP/placebo. Primary outcomes not stipulated. First 3 weeks monitored as in-patients. Thereafter weekly. Diary cards and PEFR charts. Steroids tapered on a weekly basis following pre-set protocol. Spirometry daily, full lung function and methacholine challenge at baseline and 12 weeks. Routine liver function and theophylline levels monitored throughout treatment. Bone densitometry, plasma and urinary cortisol measurements made at baseline and 12 weeks.
Outcomes	Significant reductions in steroid dose in all groups. Comparison of changes between TAO/MP and MP/placebo significant. FEV1 reduced in TAO/pred ($p = 0.025$) otherwise no change in lung function. AR to methacholine improved in TAO/MP ($p = 0.01$). Symptoms reduced by 50% in TAO/MP patients ($p = 0.025$). 2 patients experienced abnormalities of liver function, one necessitating discontinuation. No overall significant changes in safety parameters.

Kamada 1993 *(Continued)*

Notes	Authors kindly responded to enquiries seeking clarification of data and allocation concealment. Complete data available for steroid doses, however small sample sizes and widely varying severity/doses made continuous analysis not feasible - treatment effects expressed as dichotomous variable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Nelson 1993

Methods	Randomised, double blind, placebo controlled, parallel group trial. Steroid tapering during 3 months prior to trial. Treatment phase for 1 year, some subjects continued on trial treatment for a second year.
Participants	75 patients enrolled, 57 completed 1 year of treatment from whom data was analysed. No demographic differences between groups. Age 21-75y. 19 male, 38 female. None of the patients were taking ICS, stipulated in entry criteria. All received theophylline. Mean (SE) dose (mg) MP at baseline; TAO/MP 30.8 (12.4); MP/placebo 32 (2.5). No data on baseline lung function given.
Interventions	Randomised to receive TAO/MP or MP/placebo over 1(2) years. TAO 250mg daily. Primary outcomes; hospitalisation, ER visits, 'acute steroid boosts', and lowest stable daily steroid dose. Methacholine challenge measured but no attempts to compare symptoms or PEFR. symptoms
Outcomes	Significant reductions in steroid dose achieved in both groups. Comparison (of changes in dose from baseline) between groups significant (p = 0.03). NS when groups compared cf changes from mean steroid requirements over preceding year. Significant reductions in admissions, ER, steroid boosts. No differences between groups for these parameters. No changes in AR to methacholine.
Notes	Authors kindly responded to enquiries seeking clarification of data and allocation concealment. Complete individual data obtained for steroid doses, no data available to allow calculation of SD for symptoms (not measured), lung function or exacerbations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

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

Study	Reason for exclusion
Andrade 1983	This randomised, crossover study was excluded as there was no attempt made to taper oral steroid in the study.
Eitches 1985	Non 'randomised controlled trial'. TAO treatment in 11 children, no control group. Improvements in lung function recorded and steroid doses reduced. Abnormalities of liver function noted in some patients. Cushingoid side effects in some patients on TAO. Less evidence of adrenal suppression after one year TAO as shown by adrenocortical stimulation tests.
Flotte 1991	Non 'randomised controlled trial'. 9 patients treated with TAO for at least 5 months. No control group. Significant reductions in steroid dose with reductions in exacerbations (steroid boosts) and hospitalisations. Despite benefits for asthma control there were significant increases in steroid related side effects.
Itkin 1970	Randomised controlled trial evaluating a mixed group of non-steroid and steroid dependent asthmatics. Improvements in measures of airway function in parallel with Cushingoid features and abnormalities in liver function (6 out of 12 patients) amongst the macrolide treated patients compared with the placebo group.
Menz 1990	Non 'randomised controlled trial'. 19 patients treated with TAO. Improvements in asthma stability on lower doses of steroids in responder sub-group. 3 patients withdrawn early as non-responders, and 5 as late non-responders.
Rosenberg 1991	Case report. Individual treated with TAO and completely weaned off methylprednisolone without loss of asthma control. However remains on inhaled flunisolide.
Siracusa 1993	Non 'randomised controlled trial'. 14 asthmatics treated with TAO and MP for an average of 13 months. 8 responders, 6 non-responders. Improvements in lung function, asthma control and steroid doses. Elevation in blood glucose on TAO. Abnormalities of liver function noted.
Spector 1974	Non 'randomised controlled trial'. 57 individuals with either asthma or bronchitis treated with TAO in cross-over trial. Sequence of treatment not randomised. Improvements in lung function noted in patients treated with MP. Abnormalities of liver function noted.
Wald 1986	Non 'randomised controlled trial'. 15 patients treated with TAO. No control group. Improvements in lung function and significant reductions in steroid dose (MP). Abnormal glucose tolerance in 3 patients and abnormalities of liver function.
Zeiger 1980	Non 'randomised controlled trial'. 16 asthmatics treated with TAO. Improvements in lung function and significant reductions in steroid doses (MP). Abnormalities in liver function and Cushingoid features noted.

DATA AND ANALYSES

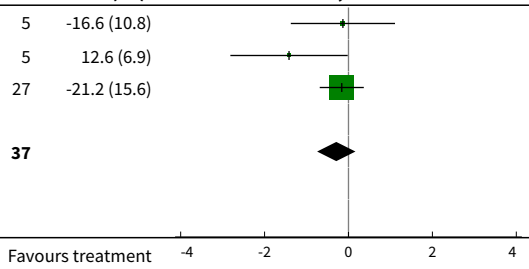
Comparison 1. Troleandomycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Steroid reduction (continuous)	3	77	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.75, 0.17]
2 Lung spirometry	2	21	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.80, 0.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Exacerbations	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Steroid reduction (dichotomous)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

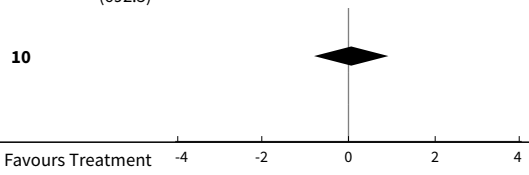
Analysis 1.1. Comparison 1 Troleandomycin versus placebo, Outcome 1 Steroid reduction (continuous).

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
Ball 1990	5	-17.9 (7.2)	5	-16.6 (10.8)		13.54%	-0.13[-1.37,1.11]
Kamada 1993	6	4.9 (2.5)	5	12.6 (6.9)		10.69%	-1.42[-2.82,-0.02]
Nelson 1993	29	-23.8 (16.8)	27	-21.2 (15.6)		75.77%	-0.16[-0.69,0.36]
Total ***	**40**		**37**			**100%**	**-0.29[-0.75,0.17]**
Heterogeneity: Tau^2=0; Chi^2=2.79, df=2(P=0.25); I^2=28.39%							
Test for overall effect: Z=1.25(P=0.21)							



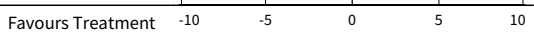
Analysis 1.2. Comparison 1 Troleandomycin versus placebo, Outcome 2 Lung spirometry.

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
Ball 1990	5	4 (8)	5	2.2 (11.7)		47.69%	0.16[-1.08,1.41]
Kamada 1993	6	289.2 (708.4)	5	309.7 (692.5)		52.31%	-0.03[-1.21,1.16]
Total ***	**11**		**10**			**100%**	**0.06[-0.8,0.92]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%							
Test for overall effect: Z=0.14(P=0.88)							



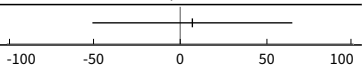
Analysis 1.3. Comparison 1 Troleandomycin versus placebo, Outcome 3 Symptoms.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Kamada 1993	6	0.3 (0.8)	5	0.4 (1)		-0.1[-1.16,0.96]



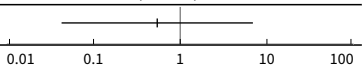
Analysis 1.4. Comparison 1 Troleandomycin versus placebo, Outcome 4 Exacerbations.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Kamada 1993	6	24 (58.8)	5	17 (38)		7[-50.65,64.65]



Analysis 1.5. Comparison 1 Troleandomycin versus placebo, Outcome 5 Steroid reduction (dichotomous).

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Kamada 1993	4/6	4/5		0.54[0.04,6.89]



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 2, 2000
Review first published: Issue 3, 2001

Date	Event	Description
25 September 2008	Amended	Search update. No new trials were found.
1 September 2008	Amended	Converted to new review format.
2 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

None

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- NHS Executive, South East, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Asthmatic Agents [*therapeutic use]; Glucocorticoids [*administration & dosage]; Randomized Controlled Trials as Topic; Troleandomycin [*therapeutic use]

MeSH check words

Adult; Humans