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Title: The effects of oral corticosteroids on lung function, type-2 biomarkers and patient-reported outcomes in stable asthma: a systematic review and meta-analysis

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Abstract

Background: Several studies have investigated the physiological effect of OCS in stable asthma, however these have included heterogeneous populations and outcomes. This paper is the first to combine their results.

Methods: We searched Medline, Embase and Web of Science databases for studies reporting the impact of OCS on FEV₁, FVC, blood eosinophils, fractional exhaled nitric oxide (FeNO), Asthma Control Questionnaire (ACQ) score or Asthma Quality Of Life Questionnaire (AQLQ) score in stable asthma. We extracted data on the correlates of OCS response.

Results: 61 studies, comprising 1,608 patients, were included. FEV₁ was improved by 9% (95% CI: 7, 11). There were stronger increases in FEV₁ among those with a mean baseline FEV₁<60% predicted (19%, 95% CI: 13, 24). Despite these improvements, substantial residual impairment remained after treatment. Blood eosinophils were reduced by 76% (95% CI: 63, 88) with larger decreases in studies of corticosteroid-naïve patients (93%, 95% CI: 73,100). Sputum eosinophils were reduced by 89% (95% CI: 79, 98) while FeNO was decreased by 35% (95% CI: 28, 41). ACQ scores were reduced by 20% (95% CI: 11, 29). Patients with higher baseline lung function impairment, sputum eosinophils, blood eosinophils and FeNO had improved OCS response.

Interpretation: OCS consistently improves lung function, reduces markers of type-2 inflammation, and alleviates asthma symptoms. However, substantial residual impairment remained following treatment and mean improvements were below the minimally important clinically difference. Patients with increased markers of type-2 inflammation are more responsive to treatment, suggesting these should be used to better target OCS use.

Background

Asthma is a common condition characterised by symptoms of cough, wheeze and breathlessness and accompanied by variable airflow obstruction and bronchial hyperresponsiveness.[1] For most patients inhaled bronchodilator(s) and/or inhaled corticosteroid treatment (ICS) are sufficient to achieve good asthma control[2], although acute exacerbations occur in all severities of asthma[2, 3], and are typically treated with a short course of high-dose oral corticosteroids (OCS) to reduce inflammation and symptoms. A minority of asthmatics do not achieve control with inhaled medications, and may be prescribed maintenance oral corticosteroids to control day-to-day symptoms and reduce exacerbations.[2]

Understanding the physiological effects of OCS is crucial to unpicking the treatment mechanism, weighing up the benefits and risks of treatment escalation prior to OCS initiation, and recognising the expected changes in an adherent patient following OCS commencement. Investigating which patients have the strongest response to OCS treatment has the potential to enable more targeted therapy, and could lead to improved patient outcomes. Several studies have previously investigated the effect of OCS, however these have included heterogeneous populations and explored various outcomes.[4-6] Systematically combining the results of these studies would lead to more complete overview of the OCS effect across all relevant outcomes, more precise estimates of the magnitude of response, and a greater understanding of how and why responses differ across patient populations.

This paper is the first to provide a comprehensive summary of studies investigating the effect of short-course or maintenance OCS treatment on lung function, biomarkers of type-2 inflammation, and patient reported symptoms in stable asthma. A secondary aim is to provide an overview of studies investigating how demographic and clinical characteristics relate to OCS response.

Methods

Search strategy and study selection

We searched the Medline (published since 1946), Embase (published since 1974) and Web of Science databases on 8th November 2018 using search terms related to oral corticosteroids and asthma to identify studies of potential interest. Full details of the electronic search strategy are given in Appendix 1.

Studies were eligible if they were published in English as peer-reviewed articles. Our review was limited to studies of stable asthma and so we excluded those of patients experiencing an asthma exacerbation (acute asthma) as these can conflate the OCS effect with the natural recovery following an acute episode. Studies using other modes of administration of systemic corticosteroids (e.g. intramuscular or intravenous) were also excluded. Our clinical outcomes of interest were FEV₁, FVC, blood eosinophils, FeNO, ACQ and AQLQ. We also extracted details on the most commonly reported measures of Type-2 inflammation: sputum eosinophils, blood eosinophils and FeNO. Titles and abstracts were screened for inclusion by two reviewers (JB and EK) and if deemed relevant according to these criteria, full-text articles were retrieved.

Data extraction and risk of bias assessment

Two reviewers (JB and EK) extracted data using a standard form. Data were extracted on the study design, intervention offered (e.g. medication name, dose, length), characteristics of patients (e.g. number of subjects, age, gender, maintenance corticosteroid use), and the effect of OCS on study outcomes. We also extracted data on the association between demographic and clinical patient characteristics and OCS response (defined by FEV₁ improvement). Study quality was assessed using the Cochrane risk of bias tool for crossover or parallel randomised controlled trials (RCTs).[7] All observational studies were deemed to be at high risk of bias due to the possibility of confounding and lack of treatment allocation blinding. To improve comparability, studies reporting baseline lung function in litres were converted to percent predicted values. We estimated the predicted FEV₁ by assuming Caucasian ethnicity and predicting the average height of the study population based on the average age and gender-specific growth charts.[8] RCTs with a non-placebo control arm were analysed as observational before-and-after studies.

Data synthesis and statistical methods

We summarised the characteristics of studies using descriptive statistics. We calculated the mean difference and its corresponding 95% confidence interval for each study. Data reported as medians

1 were treated as means, and inter-quartile ranges used to infer standard errors.[9] Subgroups were
2 combined to calculate an overall study effect and associated standard deviation.[9] When studies did
3 not report standard deviations, we imputed the median from other studies with a similar design (e.g.
4 crossover or before-and-after studies). We presented data as the percentage increase from baseline
5 as this allowed us to combine lung function results reported in both litres and percentage of predicted,
6 and preliminary analysis showed that differing baseline values were a strong contributor to inter-study
7 heterogeneity. This was calculated by dividing the mean difference, and associated 95% confidence
8 interval, by the study baseline value. Percentage decreases were constrained to be less than 100%.

9
10 We assessed statistical heterogeneity using the I^2 statistic, and used the DerSimonian-Laird random-
11 effects model used to synthesise data for all study outcomes. We conducted several pre-specified
12 subgroup analysis, investigating the effect of OCS by baseline FEV₁, maintenance corticosteroid
13 treatment, age (adult vs. child), asthma stability, intervention dose and risk of bias. We tested for
14 differences between subgroups using the chi-square significance test. We used funnel plots to explore
15 potential small study effects for outcomes comprising at least ten studies.[10] Data were analysed
16 using STATA (version 14).

Results

Study characteristics

The electronic search identified 12,849 records of which 61, comprising 1,608 patients, met inclusion criteria (Figure 1). Most studies were from the UK (n=23, 38%; Table 1) or USA (n=13, 21%). The majority were observational before and after studies (n=35, 57%), randomised parallel trials (n=14, n=23%) or randomised crossover trials (n=12, 20%). Studies generally included adults (median age=36.5, range: 11.6-59.0) and 25 (41%) had a mean baseline FEV₁>80% predicted. Studies investigated the effect of oral prednisolone (n=56, 92%) methylprednisolone (n=3, 5%) or dexamethasone (n=2, 3%), with patients most commonly receiving high dose OCS (median: 40mg, IQR: 30, 40) for around 2 weeks (median: 14 days, IQR: 7, 14).

Lung Function

FEV₁ was improved by 9% (95% CI: 7, 11; Table 2; Figure 2) following OCS, however there was substantial variability across studies (I²=74.6%). Although the vast majority of studies reported gains (n=51, 96%), eight (13%) found increases in excess of 20% from baseline. Study heterogeneity was reduced, although not negated, in subgroup analysis. We found strong evidence of a larger increase in patients with a baseline FEV₁ below 60% predicted (19%, 95% CI: 13, 24; Appendix 2) compared to an increase of only 5% (95% CI: 3, 7) in studies of patients with baseline FEV₁ in excess of 80% (p_{subgroup}<0.001). There was some evidence of a stronger effect in studies where patients received 40mg of OCS daily (11%; 95% CI: 8, 13; p_{subgroup}=0.003), among studies of patients with uncontrolled asthma (11%; 95% CI: 9, 14; p_{subgroup}<0.001; Appendix 3), and in studies of children aged less than 18 years (12%; 95% CI: 7, 17; p_{subgroup}<0.001). There was insufficient evidence to conclude differential effects based on maintenance corticosteroid treatment.

Despite the widespread improvements in FEV₁ following OCS, significant residual impairment often remained. In the 19 studies of patients with a FEV₁ % less than 80% at baseline, 14 (74%) remained below this threshold after OCS treatment. Similar results were found for studies reporting FEV₁ measurements in litres (data not shown). There was no evidence of a placebo effect for FEV₁, with an overall difference of 1% (95% CI: -1, 2) in the eleven studies reporting data on patients receiving a placebo.

Overall, FVC increased by 5% (95% CI: 3, 7; Appendix 4) although again, substantial heterogeneity existed across studies (I²=71.1%), with one reporting an extremely large increase of 16% (95% CI: 10, 22). There was little evidence of differential effects across study subgroups.

Correlates of OCS response

Several studies (n=15) investigated the predictors of OCS response on FEV₁. Six explored the effect of baseline FEV₁ [5, 11-15], with most reporting negative associations[5, 11, 13-15] including three that reached statistical significance.[5, 11, 15] In contrast, a single study reported a substantially higher mean baseline FEV₁ among corticosteroid responders (74%) than non-responders (55%).[12] A lower FEV₁/FVC ratio was associated with a stronger OCS response in two studies[5, 13], with one reaching statistical significance.[5] Two studies reported that patients with greater bronchodilator reversibility exhibited a stronger OCS response[13, 14], however a further two found little evidence of an effect.[5, 12]

Higher sputum eosinophils were consistently associated with significantly greater OCS response in five studies.[5, 6, 13, 16, 17] Similarly, a strong statistically-significant positive association between blood eosinophils and OCS response was reported in three studies.[5, 6, 18] Higher baseline FeNO was also associated with a stronger OCS response in three studies[5, 17, 18], although one reported inconclusive results.[12] A smaller number of studies have reported a significantly larger OCS response among CS non-users (n=2)[14, 15], patients with higher symptom scores (n=1)[5], and those with later onset asthma (n=1).[5] There was little evidence that other factors including age (n=4)[5, 12-14], smoking status (n=3)[16, 19, 20], sputum neutrophils (n=2)[5, 13], atopy (n=2)[5, 12], gender (n=2)[5, 12], IGE (n=1)[12] or race (n=1)[14] influenced OCS response.

Biomarkers of type-2 inflammation

Blood eosinophils were reduced by 76% (95% CI: 63, 88; Figure 3) across all studies. Moderate heterogeneity existed between studies ($I^2=34.1\%$) with blood eosinophils effectively eradicated (>95% reduction) in 4 (40%) studies. In all but one study (91%), the mean blood eosinophils following OCS was lower than 150 cells/ μ l. Further analysis revealed the largest reductions were observed in studies of corticosteroid-naïve patients (93%, 95% CI: 73, 100; Appendix 5), compared to those where at least some patients were taking maintenance ICS (78%; 95% CI: 56, 100) or OCS (60%, 95% CI: 27, 93). The smallest reduction of 41% (95% CI: 15, 66) was observed in a study where all patients were receiving at least 10mg of maintenance OCS daily.[18]

Sputum eosinophils were reduced by 89% (95% CI: 79, 98; Figure 3), with decreases of in excess of 80% reported in eight (80%) studies. Mean sputum eosinophils were less than 3% in nine (90%) studies following OCS, and less than 1% in six studies (60%). There was some inter-study heterogeneity

($I^2=15.1\%$) with one reporting a smaller, although highly uncertain, reduction of 25% (95% CI: -122, 100) in sputum eosinophils following treatment.

Overall, FeNO was reduced by 35% (95% CI: 28, 41; Figure 3) after OCS. There was little variation between studies ($I^2=0\%$), with the vast majority of study estimates ($n=10$; 91%) between a 28% and 48% reduction. In all three studies of patients with high baseline FeNO ($>50\text{ppb}$), mean values remained substantially elevated ($>30\text{ppb}$) following OCS treatment.

Patient reported outcomes

All studies ($n=9$) reported a lower ACQ score following OCS, with an overall reduction of 20% (95% CI: 11, 29; Figure 4). In the five studies where patients would be considered uncontrolled at baseline based on an $\text{ACQ}>1.5$, only 1 (20%) was below this threshold following treatment. Four studies (44.4%) reported a reduction of at least 0.5 points in the mean ACQ score following OCS. There was moderate heterogeneity ($I^2=33.4\%$), however no significant differences were observed between subgroups. Only two studies investigated the effect of OCS on AQLQ, with an overall estimated increase of 6% (95% CI: 2, 9; Appendix 6).

Risk of bias and small study effects

The randomised studies included within the review were generally of very high quality, with 20 (77%) deemed at low risk of bias (Appendix 7). Four cross-over trials[21-24] were deemed at moderate risk of bias due to insufficient detail on their randomisation procedure. Two studies[25, 26] were considered to be at serious risk of bias due to insufficient washout periods of only one week between the intervention and placebo treatment periods. Our conclusions were unchanged when restricting our analyses to studies at low risk of bias however heterogeneity was greatly diminished (Appendix 8). For example, minimal inter-study heterogeneity existed for studies at low risk of bias reporting FEV_1 ($I^2=0.8\%$) when compared to those at moderate or high risk of bias ($I^2=80.9\%$). Estimated increases in FEV_1 were higher among studies at a moderate or high risk of bias (12%; 95% CI: 9, 15) than those at low risk of bias (5%; 95% CI: 4, 7) however this was largely driven by these studies recruiting patients with a lower baseline lung function (median baseline FEV_1 %: 67.7% vs. 83.7%). These differences were largely eradicated when stratifying by baseline lung function (Appendix 8).

There was some evidence of small study effects in studies investigating change in FEV_1 (Appendix 9), with several outlying studies reporting relatively extreme values favouring the effect of OCS, yet these were not replicated for placebo. There was little evidence of small study effects in the funnel plots of

- 1 other outcomes; however, this may reflect lower power due to a smaller number of studies (data not
- 2 shown).

Discussion

Summary of main findings

In this first systematic review of patients with stable asthma treated with OCS, comprising 61 studies and 1,608 patients, we found that OCS consistently improved lung function, reduced measures of type-2 inflammation, and improved patient reported-symptoms. We found substantial heterogeneity in the magnitude of FEV₁ improvement, although this was largely resolved when restricting to studies at low risk of bias, and was partially explained by a greater response in studies of patients with lower baseline FEV₁, with uncontrolled asthma and among those receiving a higher treatment dose. Despite these improvements, there was significant residual impairment in most studies following OCS treatment. Several studies have investigated demographic and clinical predictors of improved OCS response, however consistent associations were only found for patients with higher baseline lung function impairment, sputum eosinophils, blood eosinophils and FeNO.

Lung function

The mean improvement in FEV₁ after OCS was 9%, however clinicians should expect stronger responses among patients with lower baseline FEV₁, unstable asthma or when treating children. Previous work has defined the minimally clinically important difference as 10.4% for FEV₁, suggesting that OCS is likely to lead to a clinically important difference among those with a low baseline FEV₁ (<60% predicted), but not among those with less severe baseline impairment.[27] Evidence from the studies included in this review demonstrates that patients with increased markers of type-2 inflammation are more responsive to treatment, suggesting that alignment of OCS therapy with an easily measured biomarker could lead to more targeted treatment and improved patient outcomes. The vast majority of studies in our review investigated the effect of relatively short-courses of prednisolone less than 4 weeks duration. However one Turkish study[28] did not find any significant increase in FEV₁ after 52 weeks of prednisolone compared to 16 weeks, suggesting that the full benefit of OCS on lung function is realised relatively quickly following OCS initiation. Data from one UK based study of OCS-dependant asthmatics suggests that spirometry measures return to baseline levels around one month post-intervention indicating that the lung function benefits of OCS do not extend long after discontinuation.

Biomarkers of type-2 inflammation

In the vast majority of studies, the mean blood eosinophil count was less than 150 cells/ μ l, FeNO less than 30ppb, and sputum eosinophils less than 3% following OCS treatment. High levels of these biomarkers have been consistently linked with poor asthma control, suggesting that OCS initiation

may improve health outcomes in some asthmatics.[29-31] The studies included in this review contained insufficient follow-up to determine the effect of OCS on exacerbations. However, others have previously demonstrated lower exacerbations when patients are managed using strategies targeting reduced biomarkers, suggesting that some reduction in exacerbation risk is possible with OCS use.[32] Blood eosinophils were substantially and consistently reduced by OCS, particularly in patients not receiving maintenance OCS, suggesting that this biomarker can be used to check adherence after OCS initiation if other methods (e.g. prednisolone assays) are unavailable. Data from one UK based study of OCS-dependant asthmatics suggests that type-2 biomarkers return to baseline levels around one month post-intervention demonstrating the strong temporal correlation with OCS use, and confirming their utility as a marker of adherence. Our finding of a profound reduction in blood and sputum eosinophils following OCS, and only a moderate reduction in FeNO, is consistent with OCS being a more potent inhibitor of the IL-5 than IL-4/IL-13 pathway.[33, 34]

Patient reported outcomes

OCS had a modest effect on patient-reported symptoms, with less than half of studies reporting an improvement in excess of the minimally clinically significant difference of 0.5 ACQ points.[35] Furthermore, studies of uncontrolled patients (based on ACQ score) were rarely adequately controlled following OCS, with mean post-treatment scores remaining above the commonly-used 1.5 score threshold.[36] Data from one UK based study of OCS-dependant asthmatics suggests that patient-reported outcomes return to baseline levels around one month post-intervention, suggesting that benefits of OCS on asthma symptoms are not prolonged following treatment withdrawal. Our finding of only moderate improvements in patient reported symptoms in most studies, despite maximal suppression of type-2 inflammation biomarkers, suggests that novel therapies targeting the type-2 cytokine axis are unlikely to prove a panacea in the treatment of refractory disease.

Unanswered questions

There was no long-term data on the effect of OCS on type-2 biomarker or patient-reported outcomes, and only limited data for lung function. Therefore, it remains unclear if the results we have observed are representative of the benefits that would be seen in patients who are committed to long-term OCS maintenance therapy. Similarly, data on the longer-term trajectory of study outcomes following withdrawal of the OCS was derived from a single study of OCS-dependant asthmatics.[34] It is unclear if these findings can be applied to a broader asthma population on lower levels of maintenance treatment.

Our study did not include patients with acute asthma. However, studies of OCS use in this patient population have also demonstrated significant improvements in FEV₁, blood eosinophils and sputum eosinophils following treatment.[37-39] In accordance with our findings, one study in acute asthma found moderate reductions in FeNO following OCS, and concluded that around 4-8 weeks is required for type-2 biomarkers to return to baseline levels after treatment withdrawal.[38] None of the studies included in our review involved patients on biologic therapies; this offers an important area for future research given the increasing availability of these medications.

Strengths and limitations

Our study is novel, being the first to systematically combine the results from a diverse range of studies exploring the effect of OCS. It provides a comprehensive summary of several important outcomes, and offers an at-a-glance overview which should prove useful to all prescribers of OCS. Combining data from several studies into a single analysis allowed more precise estimates of OCS effect, particularly for FeNO and ACQ score where inter-study heterogeneity was low. Contrasting across all published studies enabled detection of potential small study effects for FEV₁. Our narrative summary describing the predictors of OCS response could help enable targeted OCS treatment towards patients who would benefit most.

The primary weakness of our review was the inclusion of observational studies which may have led to increased heterogeneity. Reassuringly, our conclusions were unchanged when restricting to higher-quality randomised controlled trials, and there was no evidence of placebo effects for any of our study outcomes. The generalisability of our results may have been reduced through the exclusion of studies investigating acute asthma, and due to the short courses of prednisolone typically investigated. The focus of this review was the physiological benefits of OCS, we did not aim to summarise the evidence of corticosteroid-related morbidity which have been well described in other reviews.[40, 41]

Conclusions

Oral corticosteroids consistently improved lung function, reduced markers of type-2 inflammation, and alleviated asthma symptoms. However, substantial residual impairment remained following treatment and improvements were below the minimally important clinically difference, except for those with substantial baseline impairment. Several factors are associated with OCS response, however substantial heterogeneity remained between studies. These results should lead to more informed use of oral corticosteroids among asthmatics.

1 **Abbreviations**

- 2 ACQ: Asthma Control Questionnaire
- 3 AQLQ: Asthma Quality Of Life Questionnaire
- 4 FeNO: fractional exhaled nitric oxide
- 5 FEV: forced expiratory volume
- 6 FVC: functional vital capacity
- 7 ICS: inhaled corticosteroid treatment
- 8 IQR: Inter-quartile range
- 9 OCS: Oral corticosteroids
- 10 RCT: randomised controlled trial

1 **Declarations**

2
3 **Consent for publication:** Not applicable

4
5 **Availability of data and materials:** Not applicable

6
7 **Competing interests:** JB, EK and PEP declare no conflicts of interest. AHM received personal and
8 department funds for talks and advisory board meetings and was sponsored to attend national and
9 international conferences from pharmaceutical companies that include GlaxoSmithKline, Astra
10 Zeneca, Novartis, NAPP, Boehringer Ingelheim, Roche, Chiesi. LGH is Academic Lead for the
11 Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves
12 industrial partnerships with a number of pharmaceutical companies.

13
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15
16 **Authors' contributions:** JB designed the study. JB and EK were searched the databases, screened
17 articles for inclusion, extracted study data and analysed the risk of bias. JB analysed the data. JB, EK,
18 PP, AHM, PEP and LGH interpreted the data and drafted the manuscript. All authors reviewed the final
19 manuscript.

20
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Tables and Figures

Table 1: Description of included studies

Study ID	Country	Design ^b	Stability ^c	Patients	Mean Age	Male (%)	FEV ₁ (%)	ICS %	OCS %	Medication ^d	Dose	Time ^e
Arkins (1968)[42]	USA	OBA	U	11	49.1	36.4	47.7	NS	NS	Pred	30mg	2W
Ellul Micallef (1974)[43]	UK	OBA	U	6	55.7	33.3	33.2	0	0	Pred	40mg	1D
Lightbody (1978)[44]	UK	OBA	NS	11	36.5	NS	51.6	NS	NS	Pred	30mg	3D
Settipane (1978)[45]	USA	OBA	U	9	14.0	44.4	NS	0	0	Pred	Mean: 16.8mg	15D
Willey (1984)[46]	UK	CRCT	C	20	48.9	40.0	38.4	100	100	Pred	10mg	2W, 4W
Bhagat (1985)[11]	USA	OBA	C	10	12.1	60.0	84.0	0	0	Pred	60mg	1W
Gin (1985)[47]	UK	OBA	NS	6	47.5	66.7	NS	67	0	Pred	30mg	1W
Jenkins (1988)[21]	Australia	CRCT	C	18	42.0	50.0	56.1	100	22	Pred	12.5mg	21D
Wilmsmeyer (1990)[48]	Germany	OBA	NS	12	29.9	66.7	73.3	0	0	Pred	15mg	14D
Beam (1992)[25]	USA	CRCT	C	7	32.6	100.0	84.3	0	0	Pred	50mg	1D
Wempe (1992)[23]	Netherlands	CRCT	C	12	28.8	75.0	67.7	75	0	Pred	40mg	8D
Robinson (1993)[49]	UK	PRCT	U	18	24.8	33.3	80.1	0	0	Pred	0.6 mg/kg	2W
Bosman (1994)[50]	Netherlands	CRCT	NS	17	39.1	70.6	86.0	100	0	Pred	10mg	4W
Claman (1994)[51]	USA	PRCT	NS	24	29.8	54.2	81.3	0	0	Pred	0.5mg/kg	6D
Dworski (1994)[52]	USA	OBA	NS	20	NS	45.0	92.3	0	0	Pred	>20mg	7-9D
Sher (1994)[15]	USA	OBA	NS	29	24.0	69.0	53.4	69	41	Pred	40mg	7D
Wenzel (1994)[26]	USA	CRCT	NS	14	32.5	64.2	89.0	0	0	Pred	50mg	1D
Chhabra (1995)[4]	India	OBA	C	10	23.1	60.0	41.0	100	0	Pred	30mg	1W
Robinson (1995)[53]	UK	PRCT	U	18	23.3	33.3	81.6	0	0	Pred	0.6mg/kg	14D
Yates (1995)[24]	UK	CRCT	C	6	27.2	83.3	97.0	NS	NS	Pred	30mg	3D
Bentley (1996)[54]	UK	PRCT	U	18	24.8	38.9	81.0	0	0	Pred	0.6mg/kg	14D
Djukanovic (1997)[55]	UK	PRCT	U	27	24.0	NS	88.8	0	0	Pred	10mg, 20mg	6W
Keatings (1997)[56]	UK	OBA	C	10	NS	NS	100.4	0	0	Pred	30mg	2W
Fenech (1998)[57]	Malta	OBA	C	16	NS	NS	61.1	0	0	Pred	5mg, 10mg, 15mg	3W
Wilson (1998)[58]	UK	CRCT	C	12	34.7	50.0	86.8	100	0	Pred	5mg, 10mg, 20mg	12D
Matsuse (1999)[59]	Japan	OBA	C	11	40.2	18.2	80.5	0	0	Pred	30mg	14D
Meijer (1999)[60]	Netherlands	PRCT	NS	40	28.0	35.0	80.0	68	0	Pred	30mg	14D
Wilson (1999)[61]	UK	CRCT	C	12	28.8	50.0	94.7	100	0	Pred	5mg, 10mg, 20mg	12D
Chhabra (2000)[62]	India	OBA	C	10	25.4	60.0	74.8	100	0	Pred	0.6-0.75 mg/kg	1W
Little (2000)[17]	UK	OBA	C	37	48.6	48.6	76.3	97	NS	Pred	30mg	14D
Grootendorst (2001)[63]	Netherlands	PRCT	C	22	39.4	31.8	89.6	100	0	Pred	30mg	7D
Kurashima (2001)[64]	Japan	PRCT	C	28	41.2	53.6	84.3	68	0	Pred	20mg	14D

Liu (2001)[22]	USA	CRCT	NS	10	NS	60.0	79.2	0	0	Pred	60mg	3D
Payne (2001)[65]	UK	OBA	U	31	11.9	61.3	69.8	100	32	Pred	40mg	14D
Chakir (2002)[66]	Canada	OBA	U	21	36.6	42.9	59.8	91	0	Mpred	40mg	14D
Chaudhuri (2003)[19]	UK	CRCT	C	50	42.3	72.0	69.4	100	0	Pred	40mg	14D
Gelb (2004)[67]	USA	OBA	C	10	59.0	40.0	62.0	100	0	Pred	30mg	5D
Berry (2005)[68]	UK	OBA	U	11	44.0	51.9	64.0	100	22	Pred	30mg	14D
Fukakusa (2005)[69]	Canada	OBA	NS	13	31.0	61.5	58.0	NS	0	Mpred	40mg	14D
Lex (2005)[70]	UK	OBA	U	22	11.6	63.6	70.0	100	14	Pred	40mg	14D
Nguyen (2005)[71]	UK	PRCT	C	17	23.6	NS	80.2	0	0	Pred	30mg	7D
Slats (2006)[72]	Netherlands	PRCT	C	24	29.6	37.5	87.9	100	0	Pred	0.5mg/kg	14D
Vagaggini (2007)[73]	Italy	CRCT	C	9	25.0	88.9	88.3	0	0	Pred	25mg	4D
Sutherland (2008)[74]	USA	OBA	NS	33	40.0	51.5	70.7	100	0	Pred	40mg	7D
Bossley (2009)[12]	UK	OBA	U	61	11.8	59.0	57.0	100	36	Pred	40mg	14D
Smith (2009)[75]	New Zealand	OBA	C	73	44.0	43.8	82.8	100	0	Pred	30mg	14D
Dente (2010)[16]	Italy	PRCT	C	59	58.2	37.3	68.9	100	31	Pred	0.5mg/kg	14D
Spears (2011)[76]	UK	OBA	C	43	44.6	46.5	73.5	100	0	Dmeth	6 mg/1.74m ²	14D
Goleva (2012)[14]	USA	OBA	U	19	32.4	26.3	66.5	68	0	Pred	40mg	7D
Goleva (2013)[77]	USA	OBA	NS	39	35.1	41.0	72.6	41	0	Pred	40mg	7D
Kupczyk (2013)[5]	Europe-wide	PRCT	NS	151	47.2	58.2	80.5	100	0	Pred	0.5 mg/kg	2W
Matsunaga (2013)[78]	Japan	OBA	NS	20	53.5	50.0	66.2	100	0	Pred	0.5mg/kg	14D
Spears (2013)[20]	UK	OBA	C	53	45.6	47.2	74.6	100	0	Dmeth	6 mg/1.74m ²	14D
Van der Schee (2013)[79]	New Zealand	OBA	C	25	46.0	44.0	79.8	88	0	Pred	30mg	14D
Williamson (2013)[80]	UK	OBA	NS	15	51.0	80.0	63.4	100	0	Pred	25mg	7D
Yick (2013)[81]	Netherlands	PRCT	C	12	25.0	NS	NS	0	0	Pred	0.5 mg/kg	2W
Fernandes (2014)[13]	Brazil	PRCT	C	70	46.5	27.0	70.9	100	0	Pred	40mg	2W
Gemiciglu (2016)[28]	Turkey	OBA	U	16	52.3	6.3	61.3	100	0	Mpred	Median: 8mg	5Y
Berthon (2017)[82]	Australia	CRCT	C	54	53.6	41.8	82.0	67	0	Pred	50mg	10D
Sousa (2017)[6]	USA&UK	OBA	C	82	36.5	41.5	78.8	65	15	Pred	0.5 mg/kg	14D
Busby (2019)[18]	UK	OBA	U	44	52.9	45.0	62.4	100	100	Pred	0.5 mg/kg	7D

^a NS: Not specified

^b OBA: Observational before and after; OP: Observational parallel; CRCT: Crossover randomised controlled trail; PRCT: Parallel randomised controlled trial

^c U: Uncontrolled; C: Controlled

^d Pred: Prednisolone; Dmeth: Dexamethasone; Mpred: Methylprednisolone

^e D: Day; W: Week; Y: Year

Figure 1: Study Flow Diagram

Table 2: Weighted percentage change in all study outcomes following OCS

Outcome	Studies	Patients	% Change (95% CI)	I²
FEV ₁	52	1,216	9 (7, 11)	74.6%
FVC	19	371	5 (3, 7)	71.1%
Blood Eosinophils	10	227	-76 (-88, -63)	34.1%
Sputum Eosinophils	10	277	-89 (-98, -79)	15.1%
FeNO	11	381	-35 (-41, -28)	0.0%
ACQ	9	247	-20 (-29, -11)	33.4%
AQLQ	2	45	6 (2, 9)	0.0%

Figure 2: Weighted percentage change in FEV1 following OCS. Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Figure 3: Weighted percentage change in type-2 biomarkers following OCS. Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Blood Eosinophils

Sputum Eosinophils

FeNO

Figure 4: Weighted percentage change in ACQ following OCS. Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Appendices

Appendix 1: Electronic search terms

Web of science

TS=(prednisolone OR prednisalone OR prednisone OR ((oral OR systemic) NEAR/2 (corticosteroid* OR steroid* OR glucocorticoid*))) AND TS=asthma

Medline: Ovid MEDLINE(R) 1946 to October Week 5 2018

(prednisolone OR prednisalone OR prednisone OR ((oral OR systemic) ADJ2 (corticosteroid* OR steroid* OR glucocorticoid*))).mp AND asthma

Embase: Embase 1974 to 2018 November 07

(prednisolone OR prednisalone OR prednisone OR ((oral OR systemic) ADJ2 (corticosteroid* OR steroid* OR glucocorticoid*))).mp AND asthma AND (article or review).pt

Appendix 2: Weighted percentage change in FEV₁ following OCS, stratified by baseline FEV₁^a

^a Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Appendix 3: Weighted percentage change in FEV₁ following OCS, stratified by stability^a

^a Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Appendix 4: Weighted percentage change in FVC following OCS^a

^a Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Appendix 5: Weighted percentage change in blood eosinophils following OCS, stratified by maintenance corticosteroid use^a

^a Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Appendix 6: Weighted percentage change in AQLQ following OCS^a

^a Squares indicate study-specific risk estimates (size of the square reflects the study-specific weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates summary estimate with its corresponding 95% confidence interval.

Appendix 7: Risk of bias for randomised studies

Study ID	Randomisation	Deviation	Missing Data	Outcome Measurement	Reported Result	Overall
Parallel RCT						
Robinson (1993)	Low	Low	Low	Low	Low	Low
Claman (1994)	Low	Low	Low	Low	Low	Low
Robinson (1995)	Low	Low	Low	Low	Low	Low
Bentley (1996)	Low	Low	Low	Low	Low	Low
Djukanovic (1997)	Low	Low	Low	Low	Low	Low
Meijer (1999)	Low	Low	Low	Low	Low	Low
Grootendorst (2001)	Low	Low	Low	Low	Low	Low
Kurashima (2001)	Low	Low	Low	Low	Low	Low
Nguyen (2005)	Low	Low	Low	Low	Low	Low
Slats (2006)	Low	Low	Low	Low	Low	Low
Dente (2010)	Low	Low	Low	Low	Low	Low
Kupczyk (2013)	Low	Low	Low	Low	Low	Low
Yick (2013)	Low	Low	Low	Low	Low	Low
Fernandes (2014)	Low	Low	Low	Low	Low	Low
Crossover RCT						
Jenkins (1988)	Moderate	Low	Low	Low	Low	Moderate
Beam (1992)	Low	Serious	Low	Low	Low	Serious
Wempe (1992)	Moderate	Low	Low	Low	Low	Moderate
Bosman (1994)	Low	Low	Low	Low	Low	Low
Wenzel (1994)	Moderate	Serious	Low	Low	Low	Serious
Yates (1995)	Moderate	Moderate	Low	Low	Low	Moderate
Wilson (1998)	Low	Low	Low	Low	Low	Low
Wilson (1999)	Low	Low	Low	Low	Low	Low
Liu (2001)	Moderate	Low	Low	Low	Low	Moderate
Chaudhuri (2003)	Low	Low	Low	Low	Low	Low
Vagaggini (2007)	Low	Low	Low	Low	Low	Low
Berthon (2017)	Low	Low	Low	Low	Low	Low

Appendix 8: Weighted percentage change in study outcomes following OCS, stratified by risk of bias

Outcome	Low risk of bias			Moderate / high risk of bias		
	Studies	% Change (95% CI)	I ²	Studies	% Change (95% CI)	I ²
FEV₁	18	5 (4, 7)	0.8%	35	12 (9, 15)	80.9%
<60% predicted	0	N/A	N/A	10	19 (13, 24)	74.0%
60-70% predicted	2	8 (3, 13)	0.0%	10	10 (7, 13)	13.0%
70-80% predicted	1	9 (5, 3)	N/A	9	8 (3, 12)	71.9%
>80% predicted	15	4 (3, 6)	0.0%	6	8 (2, 15)	88.4%
FVC	5	3 (0, 6)	28.0%	14	6 (4, 9)	75.1%
FeNO	2	-31 (-57, -4)	0.0%	9	-35 (-41, -28)	0.0%
Blood Eosinophils	3	-75 (-100, -44)	28.9%	7	-76 (-92, -61)	44.5%
Sputum Eosinophils	5	-82 (-100, -52)	0.0%	5	-89 (-100, -76)	51.4%
ACQ	3	-20 (-32, -9)	0.0%	6	-23 (-37, -9)	52.5%
AQLQ	0	N/A	N/A	2	6 (2, 9)	0.0%

Appendix 9: Funnel plot for studies reporting FEV1