Review: Adults who require inhaled corticosteroids benefit from a moderate starting dose

Powell H, Gibson PG. **High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children.** Cochrane Database Syst Rev. 2004;(2):CD004109.

QUESTION

In patients with asthma not treated by inhaled corticosteroids (ICSs), what is the optimum starting dose?

METHODS

Data sources: The Cochrane Airways Group register (includes studies from MEDLINE, EMBASE/Excerpta Medica, CINAHL, hand-searched respiratory journals, and meeting abstracts).

Study selection and assessment: Randomized controlled trials (RCTs) comparing 2 different doses (including step-down therapy) of the same ICS for ≥ 4 weeks in patients with oral-steroid–independent asthma.

Outcomes: Asthma symptoms, lung function, exacerbations, airway hyperresponsiveness (AHR), and asthma control.

MAIN RESULTS

Of 26 RCTs (4- to 24-mo duration) that met the selection criteria, 17 were in adults. *Step down vs constant ICS*: No significant differences were reported for FEV_1, symptoms, use of rescue medication in adults, adverse events, or asthma control. *High vs moderate ICS dose*: 2 RCTs showed an improvement for FEV_1 in the high-dose group relative to the moderate-dose group in adults (Table). No significant differences were reported for change in morning or evening peak expiratory flow (PEF), symptoms, rescue medication use, AHR in adults, or adverse events. *High vs low ICS dose*: No significant differences were reported for FEV_1, change in PEF, symptoms, rescue medication use, AHR, or adverse events. *Moderate vs low dose*: Moderate ICS doses led to a greater improvement from baseline in morning PEF (5 RCTs) and night waking (3 RCTs) (Table). No significant differences were reported for evening PEF, PEF diurnal variation, symptom scores, rescue medication use, AHR in adults, and adverse events. *2- or 4-fold difference in ICS dose*: When ICS dose was examined as a multifold increase over the comparator, the only significant difference found was for morning PEF, for which the change from baseline was greater for ≥ 4-fold and 2-fold increased ICS doses (Table).

CONCLUSIONS

In patients with asthma who require inhaled corticosteroids, an initial high dose improves FEV_1 but does not differ from moderate doses for other asthma outcomes. An initial moderate dose improves peak expiratory flow and reduces night waking more than a low dose.

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Initial starting doses of inhaled corticosteroids for asthma*

Outcomes	Comparisons	Number of RCTs	Weighted mean difference (95% CI)
FEV_1 % predicted	High vs moderate dose	2	10.3 (2.5 to 18.2)
Morning PEF (change from baseline)	Moderate vs low dose	5	11.1 (1.3 to 20.9)
Night waking	Moderate vs low dose	3	–0.29 (–0.53 to –0.06)
Morning PEF (change from baseline)	≥ 4-fold vs base dose 2-fold vs base dose	5 8	10.2 (1.8 to 18.7) 6.8 (0.75 to 12.8)

*PEF = peak expiratory flow; RCT = randomized controlled trial. All differences favor group listed first in the comparison column.

COMMENTARY

Airway inflammation is the key pathologic feature of asthma, and ICSs remain the most effective antiinflammatory medication and the cornerstone of asthma pharmacotherapy. However, some other features of asthma, such as airway smooth muscle dysfunction (manifesting as AHR), respond more slowly, and airway remodeling does not seem to respond to ICS at all. Assuming equivalence in drug potency, delivery, and airway deposition, the dose response to ICS depends on 2 major factors: the outcomes being measured and the duration of treatment. Different outcome measures will have different response times even when a constant dose is maintained. Nocturnal symptoms and rescue bronchodilator requirements can reach a maximum response in days to weeks, but morning peak flows and AHR often require many months before reaching a plateau in response (1).

The review by Powell and Gibson aims to ascertain the optimum initiating dose of ICS by pooling RCTs comparing various dose ranges. However, the multitude of study designs with differing durations and outcome measures poses important challenges. There is a paucity of studies, and pooling is hampered by heterogeneity. Few studies have been done in children. Nevertheless, the results suggest that the optimum efficacy for ICSs is achieved at a moderate dose range, with high doses suggesting an advantage of better lung function (as measured by FEV_1) in 2 studies in adults, and a possible advantage for improvement in AHR.

Since high-dose ICSs have systemic absorption and side effects, one needs to consider the tradeoff between benefits and risks. Even when clinical heterogeneity in ICS response is taken into account, this ratio has to favor initiation with and sustained adherence to moderate-dose ICS for most patients.

With increasing use of long-acting β-agonists (which are especially effective for symptom control and protection against AHR) in combination with ICSs, further studies may well favor low-dose ICS in combination therapy.

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Reference

1. **Reddel HK, Jenkins CR, Marks GB, et al.** Optimal asthma control, starting with high doses of inhaled budesonide. Eur Respir J. 2000;16:226-35.