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


Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Respirology ★★★★★☆ Paediatrics ★★★★★☆

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

METHODS

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

Study selection and assessment: randomised 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 (4–24 mo duration) that met the selection criteria, 17 were in adults. Step down v constant ICS. No significant differences were reported for FEV1, symptoms, use of rescue medication in adults, adverse events, or asthma control. High v moderate ICS dose. 2 RCTs showed an improvement for FEV1 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 v low ICS dose. No significant differences were reported for FEV1, change in PEF, symptoms, rescue medication use, AHR, or adverse events. Moderate v 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 2 or 4 fold and 2 fold increased ICS doses (table).

CONCLUSIONS

In patients with asthma who require inhaled corticosteroids, an initial high dose improves FEV1, 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.

Abstract and commentary also appear in ACP Journal Club.

Commentary

Airway inflammation is the key pathological feature of asthma with ICSs remaining the most effective anti-inflammatory medication and the cornerstone of asthma pharmacotherapy. However, some other features of asthma, such as airway smooth muscle dysfunction (manifest as AHR), respond more slowly, and airway remodelling does not seem to respond to ICSs 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. Nighttime 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 ICSs 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 FEV1) 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 taking into account the clinical heterogeneity in ICS response, this ratio has to be in favor of initiation with and sustained adherence to moderate dose ICSs 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 ICS, further studies may well favour low dose ICS in combination therapy.

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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Comparisons</th>
<th>Number of RCTs</th>
<th>Weighted mean difference (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>FEV1 % predicted</td>
<td>High v moderate dose</td>
<td>2</td>
<td>10.3 (2.5 to 18.2)</td>
</tr>
<tr>
<td>Morning PEF (change from baseline)</td>
<td>Moderate v low dose</td>
<td>5</td>
<td>11.1 (1.3 to 20.9)</td>
</tr>
<tr>
<td>Night waking</td>
<td>Moderate v low dose</td>
<td>3</td>
<td>−0.29 (−0.53 to −0.06)</td>
</tr>
<tr>
<td>Morning PEF (change from baseline)</td>
<td>≥4 fold v base dose</td>
<td>5</td>
<td>10.2 (1.8 to 18.7)</td>
</tr>
<tr>
<td></td>
<td>2 fold v base dose</td>
<td>8</td>
<td>6.6 (0.75 to 12.8)</td>
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</tbody>
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*PEF = peak expiratory flow; RCT = randomised controlled trial. All differences favour group listed first in the comparison column.