Inhaled corticosteroids and risk of pneumonia: evidence for and against the proposed association

A. SINGANAYAGAM, J.D. CHALMERS and A.T. HILL

From the Department of Respiratory medicine, Royal Infirmary of Edinburgh, Edinburgh, EH164SA, UK

Address correspondence to A. Singanayagam, Department of Respiratory medicine, Royal Infirmary of Edinburgh, 51, Little France Crescent, Edinburgh, EH164SA, UK. email: aransinga@gmail.com

Summary

Inhaled corticosteroids (ICS) are commonly used in the treatment of chronic obstructive pulmonary disease. Recent large prospective trials have reported an increased incidence of pneumonia in patients treated with ICS. Despite this, the link between ICS and pneumonia remains controversial. In this review, pro and con arguments for the association between ICS and increased pneumonia risk are discussed, drawing on evidence from experimental and clinical research.

Evidence for the association of ICS with increased risk of pneumonia

Introduction

Inhaled corticosteroids (ICS) are commonly used in the treatment of chronic obstructive pulmonary disease (COPD) and are prescribed in up to 50% of patients. They are recommended by current guidelines for use in those with severe disease (forced expiratory volume in first second (FEV1) <50% predicted) and repeated exacerbations.

Recent large prospective trials have reported an increased incidence of pneumonia in patients with COPD taking ICS that has raised concern about their use. Despite this, the link between ICS therapy and pneumonia remains controversial. This potential association is important because patients with COPD who develop pneumonia may experience worse clinical outcomes. Studies have reported increased mortality in hospitalized and ICU-admitted patients with community-acquired pneumonia (CAP) who have underlying COPD, compared with those without COPD.

Evidence for the association of ICS with increased risk of pneumonia

Experimental studies

There are no experimental studies specifically designed to examine the pathophysiological processes underlying this proposed association but some of the existing knowledge on mechanisms of corticosteroid action offers potential putative mechanisms.

There is considerable evidence to support a role for the transcription factor nuclear factor-κB (NF-κB) pathway in the host immune response. NF-κB is expressed ubiquitously and plays a key role in the expression of pro-inflammatory genes, leading to the synthesis of cytokines (e.g. tumour necrosis factor-α (TNF-α)).
alpha (TNF-α) and interleukins 4, 5, 6 and 13), adhesion molecules (e.g. ICAM-1, VCAM-1) and chemokines (e.g. eotaxin, interleukin 8/CXCL8).11–14 NF-κB is prevented from binding to DNA by the action of the inhibitors of NF-κB (IκB) protein family.14–16 The inhibitory protein IκB binds to NF-κB within the cell cytoplasm and one of the anti-inflammatory effects of corticosteroids is to increase expression of IκB and thus inhibit NF-κB.16–18

Increased markers of NF-κB pathway activity have been demonstrated from airway samples of patients with COPD and the pathway has been implicated in disease pathogenesis.19 Therefore, ICS-induced inhibition of NF-κB would appear to be a logical therapeutic strategy for patients with COPD. However, one caveat to inhibition of NF-κB is the potential suppression of beneficial host responses to micro-organisms. Studies have shown that type 1 Interferon-β and type III Interferon-γ are immunological responses induced by the presence of pathogens, in an NF-κB dependent manner, which initiate a number of complex downstream processes involved in the host defence to infection.12,20 Therefore, there may be concerns that inhibition of NF-κB by corticosteroids may have a detrimental effect by suppressing these immune responses to infectious agents in the airways. However, such mechanisms are poorly understood and studies in vitro and in animal models are required for further characterization.

There is also evidence to support a key role for the NF-κB pathway in the host response to pneumococcal infection (the most common micro-organism implicated in CAP).21 Immune receptors [such as Toll like receptor (TLR) 2 and TLR4], which activate NF-κB have been shown to be stimulated by pneumococcal infection22,23 and activation of NF-κB by pneumococcus has been demonstrated in vitro and in vivo.24–26 Targeted genetic disruption of the NF-κB p50 subunit leads to increased susceptibility to pneumococcal infection in mice.27 Furthermore, polymorphisms in the IκB gene have also been shown to be associated with protection against invasive pneumococcal disease in humans.28

The central role of NF-κB in immune responses to bacteria such as Streptococcus pneumoniae potentially offers a biologically plausible explanation for the increased risk of pneumonia associated with ICS, due to their inhibitory effects on this pathway, but at present this remains speculative.

### Evidence from Clinical studies

The majority of clinical evidence for the association between use of ICS and increased pneumonia risk has come from large randomized controlled trials (RCTs). The three largest trials, which have reported an increase in risk of pneumonia, have compared fluticasone alone (or in combination with salmeterol) with placebo or other inhaled therapies and have reported an increased frequency of pneumonia in fluticasone-containing treatment arms (alone or in combination).5–7 Table 1 summarizes characteristics of these three trials and pneumonia rates observed in the treatment and control groups.

### Table 1 Characteristics of three largest RCTs which have reported increase in pneumonia rates with ICS use

<table>
<thead>
<tr>
<th>Study</th>
<th>Medications assessed</th>
<th>Patient number</th>
<th>FEV1 % Pred, Mean (SD)</th>
<th>Trial length</th>
<th>Primary outcome</th>
<th>Pneumonia rates</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calverley et al.5</td>
<td>Fluticasone 500 μg bd</td>
<td>1534</td>
<td>44 (12.3)</td>
<td>36 months</td>
<td>All cause mortality</td>
<td>19.3% (combination)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>Placebo bd;</td>
<td>1524</td>
<td>44 (12.3)</td>
<td></td>
<td></td>
<td>18.3% (fluticasone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1533</td>
<td>44 (12.3)</td>
<td></td>
<td></td>
<td>12.3% (placebo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluticasone (500 μg)/</td>
<td>1521</td>
<td>44 (12.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>salmeterol 50 μg bd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kardos et al.6</td>
<td>Fluticasone (500 μg)/</td>
<td>507</td>
<td>40 (8.9)</td>
<td>12 months</td>
<td>Exac rate</td>
<td>4.5%</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>salmeterol 50 μg bd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmeterol 50 μg bd</td>
<td>487</td>
<td>40 (8.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedzicha et al.7</td>
<td>Fluticasone (500 μg)/</td>
<td>658</td>
<td>39</td>
<td>24 months</td>
<td>Exac rate</td>
<td>7.6%</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>salmeterol 50 μg bd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.6%</td>
<td></td>
</tr>
</tbody>
</table>

*P-value compares pneumonia rates between treatment and control groups and indicates that addition of ICS causes increased pneumonia rates.

FEV1: Forced expiratory volume in first second; Exac: Exacerbation
Two recent meta-analyses that have included the above trials and other smaller studies in the literature have both concluded that ICS therapy is significantly associated with increased risk of pneumonia.29,30 Supportive evidence also exists from studies with other methodological designs other than randomized clinical trials. A Canadian population-based cohort study used a nested case–control analysis to investigate effect of ICS use on risk of hospitalization for pneumonia.31 This was a large health database with over 175,000 patients with COPD and was used to study the frequency of ICS use in those admitted with pneumonia. ICS use was associated with a 70% increase in rate of pneumonia hospitalization with a dose–response relationship (greatest increase observed with highest doses of ICS, equivalent to 1000 mg fluticasone per day). There was no difference in all-cause mortality between patients on ICS and those who were not. The additional strength of this study was that, unlike the clinical trials described above, pneumonia risk was the specific predefined endpoint.

Summary

The large body of evidence from studies of different design, in different populations, offers strong support that ICS are associated with increased risk of pneumonia. Additionally, pre-existing knowledge about the mechanistic effects of ICS, specifically through inhibition of the NF-κB pathway, offers a biologically plausible hypothesis to add further supportive evidence for this association.

Evidence against the association of ICS with increased risk of pneumonia

Experimental studies

Use of ICS in vitro and in animal models

Studies using respiratory epithelial cell cultures have indicated that pre-incubation of tissue from normal subjects with fluticasone propionate causes a significant reduction in invasion of epithelial cells by common bacterial pathogens such as Pseudomonas aeruginosa,32 S. pneumoniae and Haemophilus influenzae.33 Animal studies have also shown that treating mice with inhaled fluticasone propionate significantly reduces invasion of Mycoplasma pneumoniae in lung tissue and suppresses lung inflammation.34 Similar findings have also been observed in a mouse model of pneumococcal pneumonia, where administration of fluticasone propionate reduced pneumococcal lung invasion by almost 50% at 24 and 48 h after infection.33 Table 2 summarizes existing in vitro and in vivo studies of ICS in lung infection.

In vitro studies and animal models do not support the proposed increased risk of pneumonia in patients with COPD on ICS therapy. In contrast, results from these experimental studies suggest that ICS therapy would be expected to reduce the risk of bacterial infection and pneumonia and thus do not provide a convincing mechanistic explanation for the proposed association.

Evidence from clinical studies

Although several clinical trials have reported increased rates of pneumonia associated with ICS use5–7 (discussed in ‘pro’ section), one major criticism is that none of these trials were designed specifically to assess risk of pneumonia and therefore do not consistently use an objective definition of pneumonia (i.e. no radiographic confirmation). A diagnosis of pneumonia is largely based on clinical judgement by investigators reporting an ‘adverse event’ of pneumonia at study follow-up (exact numbers with radiographic confirmation are not reported). Evidence suggests that diagnosis of pneumonia based on clinical symptoms and signs alone is unreliable35 and since the clinical presentation of COPD exacerbation and pneumonia may overlap considerably, without radiographic confirmation, an adverse event could potentially be misclassified as pneumonia rather than exacerbation (and vice versa). This raises doubt over whether a true increase in pneumonia has been observed in these

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental model</th>
<th>Micro-organism</th>
<th>Effect of ICS</th>
</tr>
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<tbody>
<tr>
<td>Dowling et al.32</td>
<td>In vitro—human nasal epithelial cells</td>
<td>P. aeruginosa</td>
<td>Reduced bacterial invasion and mucosal damage</td>
</tr>
<tr>
<td>Barbier et al.33</td>
<td>In vitro—airway epithelial cells</td>
<td>S. pneumoniae and H. influenzae</td>
<td>Reduced bacterial invasion in vitro and in vivo</td>
</tr>
<tr>
<td>Chu et al.34</td>
<td>In vivo—murine model</td>
<td>M. pneumoniae</td>
<td>Reduced bacterial invasion and airway inflammation</td>
</tr>
</tbody>
</table>
trials. Future prospective RCTs of inhaled corticosteroids with a prespecified outcome of development of pneumonia, using objective criteria (including radiographic confirmation) are now needed to provide further clarification.

Another potential confounding factor, which may cast doubt over whether a true increased pneumonia risk exists is the use of antibiotics in the treatment and control groups in these studies. Two of the largest trials showed that use of an ICS containing regimen led to a reduction in exacerbations of COPD. A large proportion of these exacerbations are likely to be infective and thus would have been treated with antibiotics by the investigators. Since the control groups in these studies had significantly more frequent exacerbations than the ICS groups, they may have received more courses of antibiotics. Although this was not the case in one trial, where antibiotics were actually shown to be more frequently prescribed in the ICS arm, it is unclear from the data presented by other trials and antibiotic usage is not a factor that is controlled for in any of the existing meta-analyses. Bacterial load is known to correlate with airways inflammation and treatment with antibiotics has been shown to reduce bacterial load in patients with COPD. Therefore, the increased pneumonia rates seen in the ICS groups in these trials could be due to the confounding factor of fewer antibiotic courses being given to these patients during the course of the trial rather than a true cause–effect relationship. Future studies and meta-analyses should adjust for antibiotic usage, to characterize this further.

Despite ICS use being associated with increased pneumonia risk in these trials, there has not been a reported increase in overall mortality in any of the clinical trials. This may be considered by some to be an unexpected finding, on the basis of studies, which suggest that patients with COPD who are hospitalized with pneumonia have higher mortality rates than those without COPD, although others have shown the opposite and this remains a controversial area. Previously, it had been suggested that the absence of an increase in mortality in these trials may have been due to the mixture of opposing effects of reduced exacerbations and increased pneumonia observed (resulting in no overall net difference in survival). However, a post hoc analysis of the TORCH study has characterized this further by showing that, although rates of pneumonia were higher in the groups receiving fluticasone or combination fluticasone/salmeterol, there was no difference in pneumonia-related serious adverse events (death or hospitalization) between the fluticasone, combined fluticasone/salmeterol and placebo groups. This observation suggests that either episodes of pneumonia associated with ICS use are mild in severity (perhaps ICS use increases risk of pneumonia but protects against severe pneumonia and pneumonia-related complications) or may reflect the fact that certain subgroups of COPD patients in these trials benefit from ICS, while others may be harmed (resulting in no net difference in survival).

There have been some suggestions that the risk of pneumonia with ICS may be dose dependent or related to only certain classes of ICS. Differences exist in the pharmacological actions and metabolism of different ICS, with budesonide being more rapidly cleared from airways than higher potency ICS such as fluticasone. The largest trials have assessed the more potent ICS fluticasone propionate. However, a recent meta-analysis by Sin et al. which included only studies assessing budesonide, a lower potency ICS, found no increase in pneumonia rates associated with its use. This contrasts with the results of two other meta-analyses that did not separate out class or strength of ICS when considering studies for inclusion and were more heavily influenced by studies using fluticasone. Case–control studies have also suggested that the risk of pneumonia with ICS may be dose dependent and therefore further separate assessments of trials involving individual classes of ICS (e.g. fluticasone, beclomethasone etc.) are now required to explore this theory.

Several population-based studies have identified risk factors for development of CAP, and although many have found a history of COPD to be an independent risk factor for pneumonia, very few have separated out the influence of treatments to examine whether ICS use is an independent risk factor. A large Spanish study of 1336 patients with confirmed CAP showed that use of ICS was associated with CAP in bivariate analysis but was not independently associated after adjustment on multivariate analysis. However, only a small proportion of patients in this study were taking ICS therapy (8.8% in group with CAP vs. 3.0% in control group). The advantage of this study is that all patients included had radiologically confirmed pneumonia, thus eliminating the possibility of clinical overlap with COPD exacerbations. However, the fact that this study did not find ICS use to be an independent risk factor for pneumonia goes against the proposed association.

**Summary**

Although several clinical trials have reported increased pneumonia risk with ICS, there are problems with the reliability of this conclusion, largely
due to the fact that none of the trials were specifically designed to assess this outcome. This issue will remain unresolved, until a large prospective trial is conducted, which uses objective criteria for definition of pneumonia. Furthermore, studies using ICS in vitro and in animal models do not support an association with increased pneumonia and suggest that ICS should reduce bacterial invasion into lung tissue. In combination, this evidence casts considerable doubt over whether ICS use in COPD is truly associated with increased pneumonia risk.

Conclusions
To date, the link between ICS therapy in COPD and increased pneumonia risk is unclear and evidence from experimental and clinical studies discussed above is conflicting. Table 3 summarizes evidence for and against the proposed association. ICS have well documented benefits to patients with COPD including a reduction in frequency of acute exacerbations and also an improvement in patient health-related quality of life (St George’s respiratory questionnaire). Therefore, the potential increased pneumonia risk should be carefully balanced with the favourable effects that ICS therapy can offer and at present, existing evidence is by no means conclusive. Further experimental and clinical studies are needed.

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Conflict of interest: None declared.

References

Table 3 Evidence for and against association of ICS and pneumonia from experimental and clinical studies

<table>
<thead>
<tr>
<th>Evidence supporting association of ICS with pneumonia</th>
<th>Evidence against association of ICS with pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologically plausible link—through inhibition of NF-kB by ICS.</td>
<td>In vitro and in vivo studies using ICS show reduced bacterial invasion.</td>
</tr>
<tr>
<td>Several large prospective trials report increased pneumonia associated with ICS use.</td>
<td>Clinical trials not designed to assess pneumonia risk and no radiographic confirmation of pneumonia.</td>
</tr>
<tr>
<td>Case–control study showing increased risk of pneumonia hospitalization with ICS use.</td>
<td>ICS not identified as an independent risk factor for pneumonia in a population based study.</td>
</tr>
<tr>
<td>Two separate meta-analyses showing increased risk of pneumonia associated with ICS use in pooled analysis.</td>
<td>Meta-analysis restricted to budesonide trials did not find a link with pneumonia.</td>
</tr>
</tbody>
</table>

Conflict of interest: None declared.


41. Rees PJ. Inhaled corticosteroids do not reduce mortality but increase pneumonia in COPD. *Evid Based Med* 2009; **14**:74.


