Difference between patient-reported side effects of ciclesonide versus fluticasone propionate

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Adverse events; Inhaled corticosteroid questionnaire; ICQ; Patient-reported outcomes

Summary
Rationale: Patient-reported outcomes provide new insights into the dynamics of asthma management. Further to asthma control and quality of life, self-reported side effects of treatment can be assessed with the validated Inhaled Corticosteroid Questionnaire (ICQ).
Objectives: To compare patient-reported side effects between the inhaled corticosteroids ciclesonide and fluticasone propionate.
Methods: Patients with moderate or moderate-to-severe asthma, pre-treated with a constant dose and type of medication, were randomized in three separate studies: 1) once daily ciclesonide 320 μg (n = 234) or twice daily fluticasone propionate 200 μg (n = 240); 2) twice daily ciclesonide 320 μg (n = 255) or twice daily fluticasone propionate 375 μg (n = 273); and 3) twice daily ciclesonide 320 μg (n = 259) or twice daily fluticasone propionate 500 μg (n = 244). Patients rated the side effect questions of the 15 domain ICQ on a 7-point Likert scale (0 = not at all, 6 = a very great deal) during scheduled visits.
Results: The majority of side effect scores remained similar with ciclesonide but worsened statistically significantly with fluticasone propionate from baseline to the end of the study in within-treatment analyses. In between-treatment analyses of studies 1 and 3 ciclesonide significantly improved total side effect scores (p < 0.025) and 14 out of 30 individual local and systemic domain scores (p < 0.025) compared with fluticasone propionate. In Study 2, although ciclesonide improved the majority of scores compared with fluticasone propionate only ‘oropharyngeal itching’ reached statistical significance (p < 0.025, one-sided).

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Dr Caeser was an employee of Nycomed GmbH at the time the studies were conducted and now works as a self-employed healthcare consultant.

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Introduction

Inhaled corticosteroids (ICS) are accepted worldwide as the recommended first-line treatment for persistent asthma of all severities in both adults and children. However, many patients perceive relatively mild side effects even with low-dose ICS. Although patients often do not mention these mild side effects during consultation, the consequences of side effects are not trivial as quality of life can be significantly affected and treatment compliance reduced. The extent of patient-perceived side effects related to ICS use is likely to be underestimated in daily clinical practice.

Today, patient-reported outcomes are increasingly combined with traditional clinical data in order to form a comprehensive assessment of how asthma treatment and management can be tailored to patient-focused care. Patients’ perception of their quality of life and symptom control can yield important information unattainable from routine clinical testing and may provide evidence of a treatment benefit from a patient’s perspective.

Further to quality of life and asthma control questionnaires, the Inhaled Corticosteroid Questionnaire (ICQ) has been developed to measure the prevalence and intensity of patient-perceived side effects. The ICQ has been validated, and its reliability, reproducibility and responsiveness to increasing ICS dose have been reported. Recent clinical studies of ICS safety have shown improved systemic and local safety profiles with ciclesonide versus fluticasone propionate. We hypothesise that patient-based outcomes could reveal more precisely the side effect profile of ciclesonide compared with fluticasone propionate from the perspective of the patient than traditionally spontaneously reported side effects. Here we present the findings from the first three clinical studies comparing the patient-reported side effects of ciclesonide with fluticasone propionate in patients with moderate or moderate-to-severe asthma, as measured by the ICQ.

Methods

Patients

In three separate studies, patients aged 12–75 years with a history of bronchial asthma, as defined by the American Thoracic Society, for >6 months but otherwise in good health were included if they had been pre-treated with a constant dose and type of asthma medication (except rescue medication). All participants had reversible airway obstruction, i.e. an improvement in forced expiratory volume in 1 s (FEV₁) ≥12% of initial and ≥200 mL after inhaling 200–400 μg salbutamol, prior to randomization. Appendix 1 contains further information on inclusion and exclusion criteria.

Study design

All studies had a multicentre, randomized, parallel-group design (Table 1). Prior to randomization and at each scheduled visit correct inhaler technique was reviewed. No spacer device was used for study-drug administration. Patients were randomized as follows: study 1) ciclesonide (CIC) 320 μg once daily or fluticasone propionate (FP) 200 μg twice daily; study 2) CIC 320 μg twice daily or FP 375 μg twice daily; and study 3) CIC 320 μg twice daily or FP 500 μg twice daily. CIC was administered via metered-dose inhaler (MDI) in all studies. FP was administered via dry powder inhaler (DPI) in Study 1 and via MDI in Studies 2 and 3. Patients were blinded to medication in Study 3. Salbutamol (100 μg/puff) was used as rescue medication throughout all studies. Suspected fungal infections of the mouth or throat were confirmed in the laboratory. Patients recorded treatment compliance in daily diaries. All studies were performed in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki in its revised form (Somerset West 1996). The protocols were approved by the relevant Independent Ethics Committee or Institutional Review Board for each participating centre. Before recruitment into the studies, all patients gave written informed consent. For adolescents taking part in the studies, their legal representative also gave written informed consent.

For more information regarding the methodologies of these studies, we refer the reader to the respective publications.

Patient-reported side effect assessment

The ICQ consists of 57 side effect-related questions grouped into 15 domains covering both oropharyngeal and systemic side effects (Appendix 2). Patients completed the ICQ at baseline, and after 4 and 12 weeks of treatment in Study 1; at baseline and after 8, 16 and 24 weeks of treatment in Study 2; and during run-in, at baseline and after 4, 8, 12, 16, 20 and 24 weeks of treatment in Study 3. At all time points, patients assessed their experiences with asthma medications over the previous 2 weeks.

Patients rated the questions on a 7-point Likert scale from 0 (not at all) to 6 (a very great deal). The scoring rules recommended by the ICQ authors were followed. The raw scores of the ICQ were transformed into 15 domain scores on a scale from 0 (none) to 100 (worst possible). All
Data are presented as median (range).

Beclometasone dipropionate equivalent. CIC demonstrated, then superiority (one-sided per-protocol analysis) of CIC in comparison with FP was tested. In Study 3, superiority of CIC versus FP was tested. The ICQ questionnaire was not a primary outcome and no statistical analyses were performed.

Results

In all three studies asthma control was maintained in both the CIC and FP groups; for additional results we refer the reader to the published clinical studies for the efficacy and investigator-recorded safety results.\textsuperscript{15,19,20}

Table 1: Summarized study details and selected baseline and patient characteristics of the intention-to-treat population in the three studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Run-in period (weeks)</th>
<th>Run-in medication</th>
<th>Asthma severity</th>
<th>Treatment period (weeks)</th>
<th>Design of study</th>
<th>Study treatment</th>
<th>Sex (n):</th>
<th>Age, years\textsuperscript{a}</th>
<th>FEV\textsubscript{1}% predicted at T\textsubscript{0}\textsuperscript{b}</th>
<th>Reversibility (%) at T\textsubscript{0}\textsuperscript{b}</th>
<th>Prior ICS dose (\textmu g/day) at T\textsubscript{0}\textsuperscript{b,c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N = 474)</td>
<td>1–4</td>
<td>FP &lt;250 \mu g, or equivalent</td>
<td>Moderate</td>
<td>12</td>
<td>Randomized, open-label, parallel-group</td>
<td>CIC 320 \mu g once daily</td>
<td>Female</td>
<td>38 (12–73)</td>
<td>88.2 ± 15.4</td>
<td>19.6 ± 8.6</td>
<td>491 ± 173</td>
</tr>
<tr>
<td>2 (N = 528)</td>
<td>2</td>
<td>FP 500–1000 \mu g, or equivalent</td>
<td>Moderate-to-severe</td>
<td>24</td>
<td>Randomized, open-label, parallel-group</td>
<td>CIC 320 \mu g twice daily</td>
<td>Male</td>
<td>40 (12–74)</td>
<td>90.4 ± 13.8</td>
<td>19.6 ± 8.4</td>
<td>506 ± 201</td>
</tr>
<tr>
<td>3 (N = 503)</td>
<td>2</td>
<td>BDP ≥1000 \mu g, or equivalent</td>
<td>Moderate-to-severe</td>
<td>24</td>
<td>Randomized, double-blind, double-dummy, parallel-group</td>
<td>CIC 320 \mu g twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIC administered via MDI in all studies (CIC 320 \\mu g ex-actuator equivalent to CIC 400 \\mu g ex valve); FP administered via DPI in Study 1 (FP 200 \\mu g twice daily equivalent to a total nominal daily dose of FP 400 \\mu g) and MDI in Studies 2 (FP 375 \\mu g ex valve equivalent to FP 330 \\mu g ex-actuator) and 3 (FP 500 \\mu g ex valve equivalent to FP 440 \\mu g ex-actuator).

\textsuperscript{a} Data are presented as median (range).

\textsuperscript{b} Data are presented as mean ± standard deviation.

\textsuperscript{c} Beclometasone dipropionate equivalent. CIC = ciclesonide; FP = fluticasone propionate; BDP = beclometasone dipropionate; MDI = metered-dose inhaler; DPI = dry powder inhaler; FEV\textsubscript{1} = forced expiratory volume in 1 s; T\textsubscript{0} = randomization-to-treatment visit.

Statistical analyses

Least squares means were calculated for each of the 15 domains in each study. In Studies 1 and 2, if non-inferiority (non-inferiority margin for ICQ: +4, one-sided \( p < 0.025 \), per-protocol analysis) of CIC in comparison with FP was demonstrated, then superiority (one-sided \( p < 0.025 \), intention-to-treat [ITT] analysis) of CIC versus FP was tested. In Study 3, superiority of CIC versus FP was tested. Comparison of total and domain scores with baseline scores were performed with an analysis of covariance analogous to that used by Ebbutt and Frith.\textsuperscript{24} The overall level of significance was 5\%, two-sided (type I error of \( \alpha = 0.05 \)), which in case of a one-sided hypothesis corresponds to 2.5\%.

Therefore, within-treatment differences were significant if \( p < 0.05 \) and between-treatment differences if \( p < 0.025 \).

The ICQ questionnaire was not a primary outcome and no prospective power analysis was performed.

Patients

Baseline and patient characteristics were similar between-treatment groups for each of the three studies (Table 1). Of the 637 patients enrolled in Study 1, 474 were randomized to treatment and the ITT population for ICQ assessment consisted of 452 patients (CIC, \( n = 224 \); FP, \( n = 228 \)). In Study 2, of 658 patients enrolled, 528 patients were randomized to treatment and 498 patients were evaluated (CIC, \( n = 244 \); FP, \( n = 254 \)). In Study 3, of 614 patients enrolled, 503 were randomized (CIC, \( n = 259 \); FP, \( n = 244 \)) and 487 patients were evaluated (CIC, \( n = 250 \); FP, \( n = 237 \)). Median treatment compliance was 100\% in both treatment groups in all three studies.

Patient-reported side effect assessment

Results are presented sequentially by study. Within-treatment results reflect changes in patient-perceived side effects from baseline over the treatment period, as presented in Table 2 and Fig. 1. Between-treatment results reflect differences in patient-perceived side effects associated with CIC versus FP over the treatment period, and are presented in Figs. 2 and 3. Keys results are summarized in Table 3. Positive within- or between-treatment differences correspond to increases in patient-reported side effects.

Non-inferiority of CIC versus FP was demonstrated for the total ICQ score and all domain scores in both Studies 1
Study 3 (ciclesonide 320 μg twice daily vs fluticasone propionate 500 μg twice daily; 24 weeks)

Within-treatment results
There was no significant change from baseline to the end of the study in total score (Table 2) or the majority of domain scores in the CIC 320 μg once daily group compared with the FP 500 μg twice daily group (p < 0.025, one-sided; Fig. 3). There was no significant change in the majority of domain scores in the CIC 320 μg twice daily group compared with the FP 500 μg twice daily group (p < 0.05; Fig. 1b), with the exception of ‘mood problems’, ‘dental deterioration’, ‘opharynx problems’, ‘facial oedema’ and ‘tiredness’ scores.

Discussion
We used the validated ICQ3,13 to assess patient-reported side effects in patients with moderate and moderate-to-severe asthma treated with CIC or FP in three randomized,
controlled clinical studies. Together, these studies showed very few significant overall changes in patient-perceived side effects during the study when CIC was used (four domains significantly improved and four significantly worsened). In contrast, these studies showed significant worsening with FP (no domains significantly improved and 12, 10 and three domains significantly worsened in Studies 1, 2 and 3, respectively). Comparing CIC and FP, CIC treatment provided significant improvements in the total score, as well as in individual systemic and local side effect domains, in two of the three studies (eight and six domains in Studies 1 and 3, respectively). In Study 2, only ‘opharyngeal itching’ significantly improved with CIC compared with FP. These results are supported by studies demonstrating a lower systemic and local side effect profile of CIC compared with FP using the standard open question for spontaneous side effects reporting.15-20 This highlights the need for physicians to be aware of patient-perceived side effects when prescribing ICS or when considering switching between ICS treatments. Such patient-perceived side effects can result in reduced compliance with treatment5,25 and, subsequently, in suboptimal asthma control. The doses of ciclesonide and fluticasone investigated in the current studies were found to be equivalent for efficacy and are also in a similar range of estimated equipotent doses according to the GINA guidelines.15,19,20 We, therefore, believe it is reasonable to compare patient-perceived side effects across the current doses.

Since systemic side effects are related to both the pharmacodynamic characteristics of the drug and drug deposition, it is difficult for physicians to choose the best possible combination of ICS and inhaler device when a patient reports systemic side effects. In all three studies reported here, there was a clear trend or a significant difference for at least one systemic domain in favour of CIC. Systemic side effects associated with long-term ICS use may include cataracts and glaucoma.26,27 Interestingly, ‘vision deterioration’ significantly worsened with FP treatment in Studies 1 (12 weeks) and 2 (24 weeks), and CIC was significantly superior to FP for this side effect in Study 1 (12 weeks). In addition, higher ICS doses have been related to increased psychological side effects.28,29 Therefore, it may be important from a patient’s perspective to switch from a dose of beclomethasone dipropionate 1000 μg/day or equivalent, as used by patients prior to study enrolment, to, for example, CIC 640 μg/day, as the ‘mood problems’ domain was significantly improved in the CIC treatment group in Study 3.

Together with the ICQ data, the studies reported here also collected investigator-recorded spontaneous side effect data that have been published elsewhere.15,19,20 This gave us the opportunity to investigate whether patient-reported and investigator-recorded side effects may differ. In terms of local side effects, oral candidiasis did not occur (0%) in the CIC group, whereas it was diagnosed in nine patients (3.8%) in the FP group of Study 1, with a significant difference between the groups.15 This is reflected in the patient-reported side effect scores of Study 1 as assessed by the ICQ, since the score for the question related to oral candidiasis significantly worsened in the FP group from baseline, but did not in the CIC group, and there was a significant between-treatment difference. However,
despite significantly fewer local side effects being recorded by the investigator with CIC compared with FP in Studies 2 (dysphonia and candidiasis) and 3 (candidiasis), the improvement observed in patient-reported oral candidiasis in the CIC group compared to FP group did not reach statistical significance in these studies.

A number of factors may have contributed to the worsening in patient-reported side effects with FP treatment from baseline to the end of the study. In Study 1, the dose of ICS was higher during the treatment period than during the run-in period in both the CIC and FP groups. In all three studies, a switch to a different type of device or ICS may...
have occurred and inhaler technique was reviewed at the randomization-to-treatment visit and at each scheduled visit thereafter, which possibly resulted in higher lung deposition as the studies progressed. There were no data prior to study entry to determine any changes in compliance, but compliance was high during the treatment period of all three studies, as is often the case in trial settings. These factors are likely to have been similar in the FP and CIC treatment groups; however, the majority of patient-reported side effects did not significantly worsen from baseline to the end of the study with CIC treatment. These studies, therefore, provide important information from a patient’s perspective regarding the results of switching between ICS treatments.

It is possible that different devices may account for differences in patient-reported side effects seen between treatments in Study 1, in which CIC was delivered via MDI versus FP via DPI, but not in Study 2 or 3 where MDI was used in both arms. However, a previous placebo-controlled study comparing both MDI and DPI devices of FP suggested no differences between these devices in the investigator-recorded side effects, dysphonia, oral candidiasis and throat irritation, which were similar across all FP treatment groups. In Study 3, the daily dose of FP was higher (1000 g ex valve) than the dose of CIC (640 g ex mouthpiece = 880 g ex valve), which may partly explain the differences observed, although differences were still observed in Study 1 and 2 where microgram doses were similar. Finally, it cannot be ruled out that the open-label design of Studies 1 and 2 may also have contributed to the differences in patient-reported side effects seen between treatments.

The general limitations of all patient-reported questionnaires include respondent fatigue and measurement bias. Limitations specific to the report of side effects include the probability that the side effects experienced by the patients included in the present studies are generally mild, as patients have volunteered to participate and continued to use their ICS regardless of their perceived side effects. This so-called survival bias implies that patients in real life may experience even more side effects than those reported here and may benefit from prescription strategies that aim to avoid side effects. Moreover, a quick and reliable patient-reported method for measuring side effects, such as the ICQ, may encourage patients to become more active in the management of their asthma; patient self-management has been shown to improve quality of life and compliance. In addition, patients are more likely to report side effects when questioned specifically compared with neutral questioning.

In summary, patients with moderate and moderate-to-severe asthma treated with CIC reported significantly less intense side effects compared with patients of similar severity treated with FP, as assessed by the ICQ. These results mimic the results of the individual clinical studies demonstrating an improved side effect profile assessed by spontaneous side effect reporting of CIC in comparison with FP but the assessment with the ICQ provides more detail regarding the side effect profile. Therefore, it is, therefore, not only a need for physicians to be aware of patient-perceived side effects with respect to the dose and the application method but also the choice of the inhaled steroid prescribed.

### Competing interests

Thys van der Molen has received research grants from Merck Sharp & Dohme, GlaxoSmithKline, AstraZeneca and Nycomed GmbH and honoraria for presentations and other activities from those same three companies.
advisory boards from MSD, GlaxoSmithKline, Nycomed GmbH, and AstraZeneca. Juliet M Foster has received lecture fees of $<10,000 from Nycomed GmbH and AstraZeneca and an unrestricted research grant from AstraZeneca of $<10,000. Manfred Caeser was a full-time employee of Nycomed GmbH at the time of the study conduct. Thomas Müller is a full-time employee of Nycomed GmbH. Dirkje S Postma has served as a consultant and/or received honoraria for lectures with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Nycomed GmbH and Teeva.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2010.05.021.

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