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Changes to inhaled corticosteroid dose when initiating combination inhaler therapy in long-acting beta agonist naïve patients with asthma: a retrospective database analysis

Jordan R Covvey *Ph.D. Student*¹, Blair F Johnston *Senior Lecturer*¹, Fraser Wood *Consultant Respiratory Physician*², Anne C Boyter *Senior Lecturer*¹

¹Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral St, Glasgow G4 0RE, United Kingdom; ²Forth Valley Royal Hospital, Stirling Rd, Larbert FK5 4WR, United Kingdom

Correspondence to: A Boyter anne.boyter@strath.ac.uk

Tel: +44 (0)141 548 4594, Fax: +44 (0)141 552 2562

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Abstract:

Retrospective prescribing data were obtained from 46 general practice surgeries in NHS Scotland. Patients with asthma who were naïve to previous LABA therapy and initiated combination inhaler therapy in 2008-2009 were classified according to the ICS dose in their combination inhaler compared to the highest dose of ICS they received before initiation. Among the 685 patients (541 [79.0%] who had been prescribed an ICS previously), those originally on low-, medium- or high-dose ICS were changed to high-dose combination therapy in 122/250 (48.8%), 94/151 (62.3%) or 85/113 (75.2%) cases in each ICS dose category, respectively. These results suggest that evaluation of appropriate high-dose ICS prescribing in general practice is needed.

Main text:

INTRODUCTION:

Management of chronic asthma in the United Kingdom (UK) is guided by a step-wise approach recommended by the British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN) guideline.[1] Combination therapy with an inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) is the preferred treatment at step 3, when the use of an ICS alone is insufficient for the control of persistent asthma, which is defined by the presence of symptoms, their effect on the patient's quality of life, and the future risk of adverse events such as exacerbation.[1] Previously, escalation of ICS dose was advocated to achieve optimal control, however, major international guidelines now agree on the therapeutic benefits of adding LABA therapy to ICS therapy.

The appropriate use of combination therapy has also been questioned. Breton, *et al.* described the prescribing of combination therapy against the current Canadian asthma guidelines and found that only 40% of patients prescribed combination therapy had received a prescription for an ICS in the preceding year.[2] However, no analyses to our knowledge have described ICS dose transitions on initiation of combination therapy in patients in general practice. The aim of this study was to describe dose changes during the transition from ICS to newly initiated combination inhaler therapy in patients with asthma.

METHODS:

A retrospective database analysis was conducted in 46 practices (~80% coverage) in the Forth Valley Health Board of National Health Service (NHS) Scotland, which serves nearly 300,000 patients in a representative area. Patients were included if they: (1) had physician-diagnosed asthma, (2) had their first prescription for a combination inhaler (fluticasone/salmeterol or budesonide/formoterol) between 1 January 2008 and 31 December 2009, (3) were naïve to LABA therapy in the year before initiation of combination inhaler therapy. The date of the first prescription for combination inhaler was considered the index date for each patient.

Doses of the ICS component in both single-agent and combination inhalers were obtained from the prescription posology and standardised to beclometasone dipropionate (BDP) according to the BTS/SIGN guideline.[1] For patients >12 years of age, low-dose ICS was defined as ≤ 400 micrograms daily, medium-dose ICS as >400 micrograms daily and ≤ 800 micrograms daily and high-dose as ICS >800 micrograms daily: for patients ≤ 12 years old, the dose cut-offs were halved.[1] Patients were assessed according to highest ICS dose they received in the year before the index date and the first dose of ICS in the combination therapy inhaler they received on the index date. Sensitivity analyses excluding patients with co-morbid COPD and looking specifically at children were also performed. The use of SABA and OCS in the year before the index date were quantified as markers of asthma symptoms and exacerbations, respectively.

RESULTS:

685 patients initiated combination inhaler therapy during the study period. The majority of patients were women (403; 58.8%) with a median age of 47 years (interquartile range: 32-62 years); 89 (13.0%) patients were concurrently listed on practice COPD registers. 541 (79.0%) patients had been prescribed an ICS inhaler in the year before the index date. BDP was the most widely prescribed ICS among patients before the index date (294; 54.1%), and fluticasone/salmeterol was the most common combination inhaler therapy choice (497; 72.6%).

The mean standardised dose of ICS before the index date was 677 micrograms compared to 1043 micrograms on initiation of combination inhaler therapy, resulting in a mean increase in dose of 354 micrograms (95% confidence interval [CI]: 302 to 407 micrograms, $p < 0.001$). Patients originally on low- or medium-dose ICS had mean dose increases of 550 micrograms (95% CI: 483 to 618 micrograms) or 275 micrograms (95% CI: 186 to 363 micrograms), respectively (both $p < 0.001$); patients originally on high-dose ICS had similar doses pre- and post-index (mean difference: 21 micrograms, 95% CI: -97 to 139 micrograms, $p = 0.723$).

When patients were classified according to ICS dose categories, patients on low-, medium- and high-dose ICS before the index date were changed to high-dose combination inhalers in 122/250 (48.8% of ICS category), 94/151 (62.3%) and 85/113 (75.2%) patients, respectively (**Figure 1**). Patients with no recorded prescribing of ICS pre-index were changed to high-dose combination inhalers in 81/144 cases (56.3%). Fifty-two patients (10.3% of those with pre-index ICS) were transitioned to a lower dose combination inhaler than their ICS dose pre-index. A small number (27, 3.9% of total) of patients had unclear prescription instructions and were excluded. Excluding the 129 patients with co-morbid COPD resulted in no significant changes in the overall classification, with an overall mean dose increase of 463 micrograms (95% CI: 406 to 520 micrograms), and high-dose combination inhalers remaining the post-index therapy choice in 321/596 patients (53.9%; comparison with the original cohort: $p=0.195$). Forty-four children were included in the analysis, with the majority (27; 61.4%) changing from low-dose ICS to low-dose combination therapy, and only 9 (20.5%) receiving high-dose combination therapy.

Overall, 649 (94.7%) and 199 (29.1%) patients had received at least one prescription for SABA or OCS in the previous year, respectively. The number of SABA inhalers prescribed was similar albeit variable regardless of baseline ICS dose, with a median of 6 inhalers/year (IQR: 2-12 inhalers/year; $p=0.145$ for comparison among ICS categories). The number of OCS courses was also similar with a median of 2 prescriptions/year (IQR: 1-3 prescriptions/year; $p=0.306$).

DISCUSSION:

This analysis demonstrates significant use of high-dose combination therapy among patients with asthma treated in GP surgeries. Widespread use of high-dose ICS in the UK has been noted previously. Thomas *et al.* found that within a prescribing analysis of over 22,000 adults/adolescents with asthma, 27% of patients received high-dose ICS, and 83.6% of them had no record of a trial of add-on therapy with a LABA or other controller therapy.[3] The present analysis found that over three-quarters of patients received ICS therapy before starting therapy with a combination inhaler, suggestive of better concordance with guideline recommendations. However, upon addition of a LABA to the therapy regimen, there was a widespread

pattern of simultaneous ICS dose escalation, with patients advancing directly to high-dose combination therapy, largely irrespective of their baseline ICS dose. This suggests not only questionable use of high-dose ICS, but also failure to follow guideline recommendations.

The dose-response relationship of ICS has been the subject of much research, although high quality evidence indicates that the therapeutic benefits of ICS are seen at doses of 200-1000 mcg BDP-equivalent daily.[4-5] Above this threshold, adverse effects of ICS such as HPA-axis suppression, osteoporosis and skin bruising are more common. Accordingly, the wide utilisation of high-dose ICS is likely to produce a poor return on investment, with an increased risk of local and systemic adverse effects traded for little gain in asthma control. Although as a database analysis, we were unable to determine the clinical reasoning underlying ICS dose changes, the patterns noted in this study should prompt further investigation into the appropriateness of high-dose ICS prescribing in UK general practice.

Fluticasone/salmeterol was most commonly used high-dose combination therapy in this analysis, but the reasons behind this are unclear. Fluticasone may be preferentially chosen for treatment due to its potency and ease of dosing regimen to achieve higher doses. A *post hoc* analysis found that of the 488 patients prescribed high-dose combination therapy, 149 (30.5%) were prescribed doses ≥ 1600 mcg daily ("very high-dose ICS"), and all but 5 of these patients received fluticasone/salmeterol. However, we also acknowledge that this prescribing may be inadvertent, and that a lack of awareness of potency differences between different ICS preparations may lead to the product being prescribed at twice the intended dose of budesonide/formoterol. Another contributing factor may be the licensing of high-dose combination therapy for the treatment of COPD. The analysis included patients with co-morbid COPD in the analysis, as this group of patients is often excluded from randomised controlled trials, despite constituting 5-20% of the asthma population. While it would be plausible that the inclusion of this patient group would inflate the use of high-dose combination therapy, the results of our sensitivity analysis showed no differences from the full cohort. However, clinicians may feel more comfortable prescribing larger doses of ICS for asthma than previously due to

widespread use of high-dose ICS in COPD, and may alter their prescribing practices for patients with asthma.

There was no discernible pattern of SABA/OCS prescribing among ICS dose categories, suggesting that patient symptoms and/or exacerbations were not primary motivators for dose increases during the initiation of combination inhaler therapy in this analysis. While symptoms and/or exacerbations may push a clinician to escalate therapy rapidly, changing a patient from no ICS therapy to high-dose combination therapy remains concerning and there is little evidence to support this approach. Our analysis did uncover some ICS dose step-down, albeit with the concurrent addition of a LABA (medium-dose ICS changed to low-dose combination inhaler). Although this was only seen in a small number of patients, it may provide some reassurance to the use of increasing doses of ICS and combination therapy.

High-dose combination inhalers were prescribed frequently in this UK cohort with asthma, even without a history of ICS treatment. Evaluation of the appropriateness of high-dose prescribing in general practice is needed and educational efforts should focus on the dose-response relationship of ICS and the risk of adverse effects when using high-dose ICS.

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Contributorship: ACB, FW and JRC were responsible for the concept of the study, BFJ for the analytical methods and JRC for handling of the data and execution of the analysis. All authors interpreted the data, wrote the manuscript, had access to the data and made the decision to submit for publication. ACB is the guarantor.

Transparency declaration: The guarantor affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Ethical approval: Departmental ethics was consulted regarding use of the database and determined that no formal review was required.

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Competing interests: All authors have completed the ICMJE unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) JRC has received support in the form of a Ph.D. studentship from the US-UK Fulbright Commission and the University of Strathclyde; (2) FW and ACB have received meeting support from with Novartis and GlaxoSmithKline, respectively; (3) ACB is a member of the steering committee for the BTS/SIGN asthma guideline; and (4) no other relationships or activities that could appear to have influenced the submitted work exist.

Data sharing: No additional data available.

Sponsor: The NHS Forth Valley Airways Managed Clinical Network provided the database utilised in this analysis, but had no role as an organisation in the conception or execution of the analysis, nor the preparation of the manuscript.

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