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Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: Effect of drug, dose, and device

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ABSTRACT

Background and aims: Little information is available on real-life occurrence of oral thrush in COPD patients treated with ICS. We investigated oral thrush incidence in COPD patients prescribed FDC ICS/LABA therapies and assessed whether it is modulated by the ICS type, dose, and delivery device.
Methods: We conducted a historical, observational, matched cohort study (one baseline year before and one outcome year after initiation of therapy) using data from the UK Optimum Patient Care Research Database. We assessed oral thrush incidence in patients initiating long-acting bronchodilators or FDC ICS/LABA therapy. We then compared different combination therapies (budesonide/formoterol fumarate dihydrate [BUD/FOR] and fluticasone propionate/salmeterol xinafoate [FP/SAL]) and devices (DPI and pMDI).
Results: Patients prescribed FDC ICS/LABA had significantly greater odds of experiencing oral thrush than those prescribed long-acting bronchodilators alone (adjusted OR 2.18 [95% CI 1.84–2.59]). Significantly fewer patients prescribed BUD/FOR DPI developed oral thrush compared with FP/SAL DPI (OR 0.77 [0.63–0.94]) when allowing for differences in prescribed doses between the drugs. A significantly smaller proportion of patients developed oral thrush in the FP/SAL pMDI arm than in the FP/SAL DPI arm (OR 0.67 [0.55–0.82]). Additionally, in the FP/SAL cohort (both DPI and pMDI), increased risk of oral thrush was significantly associated with high ICS daily dose (OR 1.97 [1.22–3.17] vs low daily dose).
Conclusions: ICS use increases oral thrush incidence in COPD and this effect is dose-dependent for FP/SAL therapies. Of the therapies assessed, FP/SAL pMDI and BUD/FOR DPI may be more protective against oral thrush.

1. Introduction

Oral thrush, also known as oral candidiasis, is a well-documented local side-effect associated with regular inhaled corticosteroid (ICS) use in patients with asthma [1–4]. It is thought to be caused by a reduced local immune response [5] or an increase in salivary glucose (which stimulates growth of *Candida albicans*

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[6]) after deposition of ICS in the oropharyngeal cavity. Many factors have been reported to influence the incidence of oral thrush in asthma, including type and dose of ICS used, mode of drug delivery, and patient compliance with medication instructions [7–11]. Although generally associated with temporary symptoms, ICS local side-effects, including oral thrush, can be clinically significant, and may affect patient quality of life and therapy adherence [3,12,13].

ICS are also prescribed for the treatment of chronic obstructive pulmonary disease (COPD) in patients with severe airflow limitation and/or at high risk of exacerbations, and are generally recommended in combination with long-acting β_2-agonists (LABAs) [14,15]. However, recent studies have found that ICS are being prescribed in COPD even more widely and frequently than would be expected from current management guidelines, particularly among less severe patients [16,17]. Despite the widespread use of ICS in this disease, there is little information on real-life occurrence and distribution of oral thrush in patients with COPD who are prescribed ICS [18–21]. The objective of this study was to investigate the incidence of oral thrush in COPD patients receiving ICS as part of their ICS/LABA combination therapy. In particular, we sought to assess whether oral thrush incidence is modulated by the type of ICS, the ICS dose, and the delivery device (dry powder inhaler [DPI] vs pressurised metered-dose inhaler [pMDI]).

2. Methods

2.1. Study design and data source

This was a historical, observational, matched cohort study utilising healthcare records from the Optimum Patient Care Research Database (OPCRD) [22]. The OPCRD is a bespoke database with focus on patient-reported outcomes that, at the time of this study, contained anonymous data for over 2.4 million patients from over 550 UK primary care practices across England, Scotland, Wales, and Northern Ireland. It contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. We examined data during a one-year baseline period (prior to the index date, defined below) for patient characterisation, and a one-year outcome period after initiation of a new or additional COPD therapy. The index date was defined as the date of first prescription for either a fixed dose combination (FDC) ICS/LABA (therapies assessed described below) or long-acting bronchodilator therapy (LABA, long-acting muscarinic antagonist [LAMA], or their combination; addition of an alternative long-acting bronchodilator was also considered as first prescription). This study design was necessary to determine the incidence of oral thrush, compared with a reference group without ICS exposure, and allow for seasonal changes in respiratory disease symptoms and related conditions. The study was conducted to standards suggested for observational studies, including an independent advisory group, use of an *a priori* analysis plan, study registration with commitment to publish, and a well-maintained and monitored study database [23].

2.2. Ethical approval

The study was conducted and is reported in compliance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; registration number: ENCEPP/SDPP/12762). OPCRD received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Its governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (http://optimumpatientcare.org/our-database/), an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, http://www.effectivenessevaluation.org/) to govern the standard of research conducted on internationally recognised databases (ADEPT approval reference for this study: ADEPT1416).

2.3. Inclusion and exclusion criteria

Patients eligible for inclusion in the study received a quality outcomes framework (QOF) code for COPD diagnosis [24], were aged ≥40 years at the index date, had at least 2 years of continuous practice data (1 year of baseline and 1 year of outcome data), and received ≥2 prescriptions of FDC ICS/LABA or long-acting bronchodilator during the outcome period (including prescriptions at the index date). Patients were excluded if in the baseline period they received ≥1 prescription for ICS, ≥1 prescription for both LABA and LAMA, maintenance oral corticosteroid prescription, or if they had a diagnostic code for any chronic respiratory disease other than COPD, asthma, or bronchiectasis.

2.4. Cohorts and treatment arms

We initially studied two cohorts of patients with COPD. The first cohort included patients that were prescribed FDC ICS/LABA combination therapy at the index date. Combination therapy included the following: budesonide/formoterol fumarate dihydrate (BUD/FOR) administered via a DPI device (Symbicort® Turbohaler®); fluticasone propionate/salmeterol xinafoate (FP/SAL; Seretide®) administered via DPI (Accuhaler®) or pMDI (Evohaler®) device; and beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FOR; Fostair®) administered via a DPI (NEXThaler®) or pMDI device. Patients prescribed BDP/FOR DPI were not included in the subsequent analyses owing to their low number. The second cohort included patients who were prescribed non-ICS therapy (any long-acting bronchodilator) at the index date, namely LABA, LAMA or their combination. The two cohorts were matched 1:1 (see below and Table S1). Before matching, in the non-ICS therapy cohort, patients could have been included more than once with different first prescriptions for LABA, LAMA or their combination.

We then conducted subset analyses dividing patients of the unmatched FDC ICS/LABA cohort according to different combination therapies (BUD/FOR DPI and FP/SAL DPI) and devices (FP/SAL pMDI and FP/SAL DPI) and matched them 1:1 (see below and Fig. S1A, B). Finally, in the FP/SAL pMDI treatment arm, we conducted a subgroup analysis of patients who were prescribed a spacer in the period comprising the baseline year, the index date, and two weeks after the index date (ensuring that spacer device use preceded the occurrence of oral thrush), and compared them with patients who were not prescribed a spacer in the same period.

2.5. Exact matching

We used matching with statistical adjustment for residual confounders (exact matching, as described in previous studies [25,26]) in order to ensure that we analysed comparable groups of patients. We compiled a list of potential matching criteria informed by expert clinical advice and previous research experience, including variables predictive of outcomes and the key baseline clinical characteristics differing between unmatched cohorts (identified using *t*-test, and Chi-Squared and Mann-Whitney U tests, as appropriate). The matching criteria (described in Table S1 and Fig. S1A, B) were then applied sequentially to produce two matched cohorts containing all possible pairings; bespoke software was used to randomly select final unique matched pairs.