Original Article

A Randomized Pragmatic Trial of Changing to and Stepping Down Fluticasone/Formoterol in Asthma

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What is already known about this topic? A few randomized trials have investigated step-down of inhaled corticosteroid therapy; however, very few have looked at predictors for response to step-down.

What does this article add to our knowledge? We identified exacerbation history in the last 12 months to be a significant predictor for exacerbations after inhaled corticosteroid/long-acting β_2 agonist therapy step-down.

How does this study impact current management guidelines? This study suggests that asthma stability for 3 months, as indicated in current guidelines and consensus documents, is likely to be insufficient to determine whether a patient is suitable for therapy step-down.

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Abbreviations used
ACQ7- 7-question Asthma Control Questionnaire
FENO- Fractional exhaled nitric oxide
FP/FOR- Fluticasone propionate/formoterol fumarate
FP/SAL- Fluticasone propionate/salmeterol xinafoate
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
LABA- Long-acting β_2 agonist
Mini-AQLQ- Mini Asthma Quality of Life Questionnaire
pMDI- Pressurized metered-dose inhaler
VAS- Visual analog scale

BACKGROUND: Guidelines recommend reducing treatment in patients with well-controlled asthma after 3 months of stability. However, there is inadequate real-life data to guide physicians on therapy change in daily practice.
OBJECTIVE: To assess asthma control after change to and step-down of fluticasone propionate/formoterol fumarate dihydrate (FP/FOR) in real-life patients.
METHODS: In a randomized controlled, pragmatic, open-label trial, 225 well-controlled patients with asthma were randomized (1:2) to maintain high-dose fluticasone propionate/salmeterol xinafoate (FP/SAL, 1000/100 μg) or switch to FP/FOR (1000/40 μg) daily for 12 weeks (phase 1). One hundred sixteen patients stable on FP/FOR at week 12 were subsequently randomized (1:1) to maintain this therapy, or stepped down to FP/FOR (500/20 μg) daily for 12 weeks (phase 2). The primary end point was the 7-question Asthma Control Questionnaire (ACQ7) score.
RESULTS: In phase 1, FP/FOR (1000/40 μg) (n = 126) was noninferior to FP/SAL (1000/100 μg) (n = 73) for ACQ7 (difference in means, −0.12; 95% CI, −0.32 to 0.09). In phase 2, FP/FOR (500/20 μg) (n = 52) was noninferior to FP/FOR (1000/40 μg) (n = 52) for ACQ7 (difference in means, 0.01; 95% CI, −0.20 to 0.22). There was no significant difference in exacerbation rate between the groups in either phase. However, 1 to 2 exacerbations in 12 months before phase 1 were associated with the occurrence of an exacerbation after step-down ($P = .007$).
CONCLUSIONS: In patients with well-controlled asthma, a change from FP/SAL to FP/FOR did not compromise asthma control. Step-down of FP/FOR was well tolerated; however, in contrast to current guidelines, our data suggest caution in stepping down patients uncontrolled in the last 12 months. Larger step-down studies are required to confirm these findings. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *ACQ7; Biomarkers; Combination therapy; Fluticasone; Formoterol; Fractional exhaled nitric oxide; Inhaled corticosteroids; Pragmatic trials; Salmeterol; Step-down; Antiasthmatic agents*

The Global Initiative for Asthma (GINA) document recommends a step-up in treatment for patients whose asthma is not controlled on low-dose inhaled corticosteroid (ICS) monotherapy to a combination of an ICS and a long-acting β_2 agonist (LABA).[1] Once asthma has been well controlled for at least 3 months, a stepwise reduction of treatment, by approximately 25% to 50% each time, is recommended such that patients should be maintained at the lowest possible dose of ICS that effectively achieves disease stability.[1] Yet these recommendations are often not implemented, leading many patients with asthma to be overtreated with high doses of ICS and LABA, which increases treatment costs and unnecessarily exposes the patients to treatment side effects.[2] Although ICS reduces exacerbations, real-life data suggest that LABA is more effective in controlling asthma symptoms.[3] It is therefore possible that even symptomatic patients who are not frequently exacerbating could be managed with lower doses of ICS without compromising asthma control.

A few randomized trials have investigated the step-down of ICS therapy[4-10]; however, very few have looked at predictors for response to step-down, and the findings from these studies have not provided conclusive answers as to who can be safely stepped down.[10-13] Importantly, none of the studies undertook simultaneous step-down of both ICS and LABA, which is highly relevant in daily clinical practice. Therefore, there is clearly a need for pragmatic evidence-based data on the effectiveness and safety of the step-down of ICS/LABA combination therapy. This may help overcome the hesitancy that clinicians experience to change or reduce treatment, particularly in those patients they have spent time and effort in stabilizing in their day-to-day practice.

The primary objective of this randomized controlled, pragmatic trial was to assess asthma control after a change from fluticasone propionate/salmeterol xinafoate (FP/SAL) to fluticasone propionate/formoterol fumarate dihydrate (FP/FOR) and then step-down of FP/FOR, for which the treatments were all delivered by a pressurized metered-dose inhaler (pMDI) with the same ICS. In addition, we sought to identify factors that might predict worsening of asthma after step-down, because such factors may guide individualized treatment decisions in a clinical setting and improve clinical outcomes.

METHODS

Study design

This was a 24-week randomized controlled, pragmatic, open-label trial (clinicaltrials.gov: NCT02388373; EudraCT: 2013-005365-39) consisting of a 12-week change phase (phase 1) followed by a 12-week step-down phase (phase 2) (Figure 1). To obtain a representative sample of real-life well-controlled adult patients with asthma, study participants were recruited from 27 primary care practices across England (between July 2014 and September 2015).

In phase 1, the investigative treatment was fluticasone propionate/formoterol fumarate dihydrate 250 μg/10 μg taken 2 puffs twice a day (hereafter indicated as "FP/FOR(1000)") (Flutiform 250 pMDI, Napp Pharmaceuticals Ltd., Cambridge, UK), and the comparator treatment was fluticasone propionate/salmeterol xinafoate 250 μg/25 μg taken 2 puffs twice a day (hereafter indicated as "FP/SAL(1000)") (Seretide 250 Evohaler pMDI, GlaxoSmithKline, Brentford, UK). In phase 2, the investigative treatment was FP/FOR 125 μg/5 μg taken 2 puffs twice a day (hereafter indicated as "FP/FOR(500)") (Flutiform 125 pMDI, Napp Pharmaceuticals Ltd.). The comparator treatment in phase 2 was FP/FOR(1000).

In phase 1, participants meeting the eligibility criteria were randomized (2:1) to either change to FP/FOR(1000) or stay on FP/SAL(1000). After 12 weeks, participants in the FP/FOR(1000) arm who had remained stable on the therapy and provided consent to continue were randomized (1:1) to either stay on FP/FOR(1000) or step down to FP/FOR(500) for 12 weeks. There was also an interim visit at week 4 of phase 2. Randomization for both phases