Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics

Jabbal, Sunny; Kuo, Chris RuiWen; Lipworth, Brian

Published in:
Clinical and Experimental Allergy

DOI:
10.1111/cea.13702

Publication date:
2020

Received: 30 October 2019 | Revised: 28 June 2020 | Accepted: 2 July 2020

DOI: 10.1111/cea.13702

WILEY

ORIGINAL ARTICLE

Asthma and Rhinitis

Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics

Sunny Jabbal | Chris RuiWen Kuo | Brian Lipworth

Scottish Centre for Respiratory Research, School of Medicine, Ninewells Hospital, University of Dundee, Dundee, Scotland

Correspondence
Brian Lipworth, Scottish Centre for Respiratory Research, School of Medicine, Ninewells Hospital, University of Dundee, Dundee DD1 9SY, Scotland.
Email: b.j.lipworth@dundee.ac.uk

Funding information
Departmental funds.

Abstract

Background: Smoking worsens underlying asthma inflammation and also induces resistance to inhaled corticosteroids (ICS). Small airways dysfunction measured by impulse oscillometry (IOS) is associated with worse control.

Objectives: We investigated the effects on small airways of adding long-acting beta-agonist (LABA) alone or with long-acting muscarinic antagonist (LAMA) to ICS in asthmatic smokers.

Methods: Sixteen current smokers were enrolled: mean age 44 year, FEV1 84%, FEF25-75 47%, R5 158%, ACQ 1.69, 20 pack year . Patients were converted to a reference ICS as HFA-BDP during initial run-in at median dose of 800 μg/day. Open label olodaterol 5 μg od (OLO) or olodaterol 5 μg/tiotropium 5 μg od (OLO/TIO) was added to HFA-BDP for median duration of 3 weeks in a randomized cross over design, including run-in and washout periods on HFA-BDP. IOS and spirometry were measured after each treatment (BDP/OLO/TIO or BDP/OLO) and at baseline after run-in and washout (BDP).

Results: After chronic dosing, IOS outcomes at trough except for R20 were all significantly improved with OLO/TIO compared to OLO. For the primary end-point of total airway resistance (as R5), the mean difference (95%CI) at trough was 0.06 (0.015-0.10) kPa/l/s, peripheral airways resistance (as R5-R20) 0.03 (0.003-0.06) kPa/l/s, peripheral lung reactance area (as AX) 0.38 (0.08-0.68) kPa/l and resonant frequency (as RF) 2.28 (0.45-4.12) Hz. FEF25-75 at trough was also better with OLO/TIO vs TIO: 0.93 (0.86 - 0.95) l/s while FEV1 was not different.

Conclusions: ICS/LABA/LAMA was superior to ICS/LABA on trough small airway outcomes in asthma patients who smoke.

KEYWORDS

asthma, pneumology, quality of life, small airways, smoking, triple therapy

The study was registered at clinicaltrials.gov as NCT02682862 and was approved by the East of Scotland Regional Ethics Committee (reference: 15/ES/0032).

1 | INTRODUCTION

Patients with asthma who smoke represent a difficult challenge for clinicians. The smoking asthmatic may be considered as a separate phenotype in view of the inherent problems with clinical management.[1] The occurrence of smoking among asthma patients is higher among those with poor control and also in relation to socioeconomic deprivation, with estimated prevalence rates of up to 20%.[2-4] Smoking worsens asthmatic inflammation, aggravates airway hyper-responsiveness and induces resistance to inhaled corticosteroid (ICS).[5-8] Pointedly, most randomized controlled trials exclude asthma patients who smoke, hence there are a paucity of data in order to provide evidenced based guidelines for this phenotype.

The small airways are often overlooked when considering asthma management.[9] This is perhaps surprising since the largest mucosal surface area of asthma inflammation is located in the distal airways. Indeed small airways dysfunction is common among all asthma severities.[10,11] Hence, strategies to target the small airways are important in order to achieve optimal outcomes in asthma. Long-term smoking in individuals with early stage COPD is characterized by prominent small airways dysfunction (SAD).[12] In some aspects, patients with asthma who smoke may be considered to be a similar in phenotype to patients with asthma COPD overlap.[13] Notably in smokers with normal spirometry, 76% have evidence of small airways abnormality detected using impulse oscillometry (IOS) or multiple breath nitrogen washout.[14]

Assessment of SAD in the clinic may be done using impulse oscillometry (IOS) which is a simple to perform effort independent test using a loudspeaker source to superimpose sound waves of different frequencies on top of normal tidal breathing.[15,16] The output of respiratory impedance comprises an in phase component of resistance (R) and an out of phase component of reactance (X). The resistance at 5Hz (R5) and 20Hz (R20) represents the total and central airway resistance respectively; hence, the difference (R5-R20) is the heterogeneity of resistance in peripheral airways.[17] The reactance at 5Hz (X5) and area under the reactance curve (AX) reflects peripheral lung compliance. R5-R20 and AX have been shown to be more closely related to asthma control than spirometry in patients with persistent asthma.[18,19]

The role of triple therapy in asthma is well established in guidelines with long-acting muscarinic antagonists (LAMA) being recommended as add on to inhaled corticosteroid and long-acting beta-agonist (ICS/LABA).[20] Once daily LAMA as tiotropium (TIO) added on to ICS/LABA in asthma has been shown to produce a 21% reduction in exacerbations and an improvement in trough FEV1 of between 88 and 111 mL.[21] Pointedly, patients were required to be either lifelong non-smokers or a pack history fewer than 10 pack years along with no current smoking in the previous year. However, in that study, no measurement was made of small airways function.

The advent of single closed triple inhalers for COPD is well established,[22] while clinical trials are ongoing in asthma. The TRIMARAN and TRIGGER studies in uncontrolled asthma compared the closed triple beclomethasone/formoterol/glycopyrroniumversus beclomethasone/ formoterol via pressurized metered dose inhaler (pMDI) twice daily showed a 12-15% reduction in exacerbations and a 57-73 mL difference in trough FEV1 as co-primary end-points.[23] This study also excluded current or ex-smokers with more than 10 pack years.

In order to fill a gap in literature, we therefore elected to evaluate in asthmatic smokers the effect of once daily ultra-long-acting bronchodilators as the LABA olodaterol (OLO) or the combination of olodaterol with the LAMA tiotropium (OLO/TIO), both delivered via the soft mist Respimat inhaler (Striverdi and Spiolto Respimat, Boerhinger Ingelhiem,Bracknell, UK), when added onto pre-existing ICS as HFA-beclomethasone dipropionate (BDP, Clenil Modulite pMDI, Chiesi, Manchester, UK). The rationale for choosing the Respimat device was that it was possible to deliver the OLO and OLO/TIO via the same device albeit in open label fashion. Hence, patients always took the same pMDI and Respimat devices for triple and dual therapy.

2 | PATIENTS AND METHODS

Patients with a known diagnosis of persistent asthma who were current smokers were enrolled, age 18-65 years, taking at least 400 μg per day of ICS (as HFA-BDP Clenil equivalent dose). Participants with a history of COPD or ACO were excluded. Patients who had an asthma exacerbation requiring systemic corticosteroids within 1 month of screening or requiring hospital admission within 3 months were also excluded.

Including screening, there were five visits in total (Figure 1). After initial screening, patients entered into a 2-4 week run-in period when LABA or LAMA were stopped and participant's ICS dose was rounded to equivalent reference ICS as HFA-BDP (Clenil Modulite pMDI). This dose of Clenil was then continued unchanged throughout the study. Other concomitant non-bronchodilator second line controllers such as leukotriene receptor antagonists, theophylline or cromones were permitted to be continued throughout the study but were withheld for 72 hours prior to each visit. Patients were allowed SABA during the study but asked to withhold it at least 6 hours prior to any study visit.

After the run-in period, patients were then randomized in cross-over fashion to receive open label treatment with either Olodaterol Respimat 2 puffs (5 μg) or Olodaterol/Tiotropium 2 puffs (5 μg/5 μg) once daily in the morning for 2-4 weeks as add on to Clenil. There was a 2- to 4-week washout period in between randomized treatment arms when patients continued on Clenil. The 2- to 4-week period was chosen to allow flexibility for patients for treatments and washout periods, given that 2 weeks are adequate to reach steady state for airway effects of olodaterol and tiotropium.

Measurements including IOS oscillometry (Jaeger Masterscreen IOS, Hoechberg, Germany), spirometry (Superspiro, Micromedical, Chatham UK) and ACQ were made at baseline after run-in and washout (on Clenil) and after the first and last dose of each randomized treatment on either BDP/OLO or BDP/OLO/TIO. IOS and spirometry

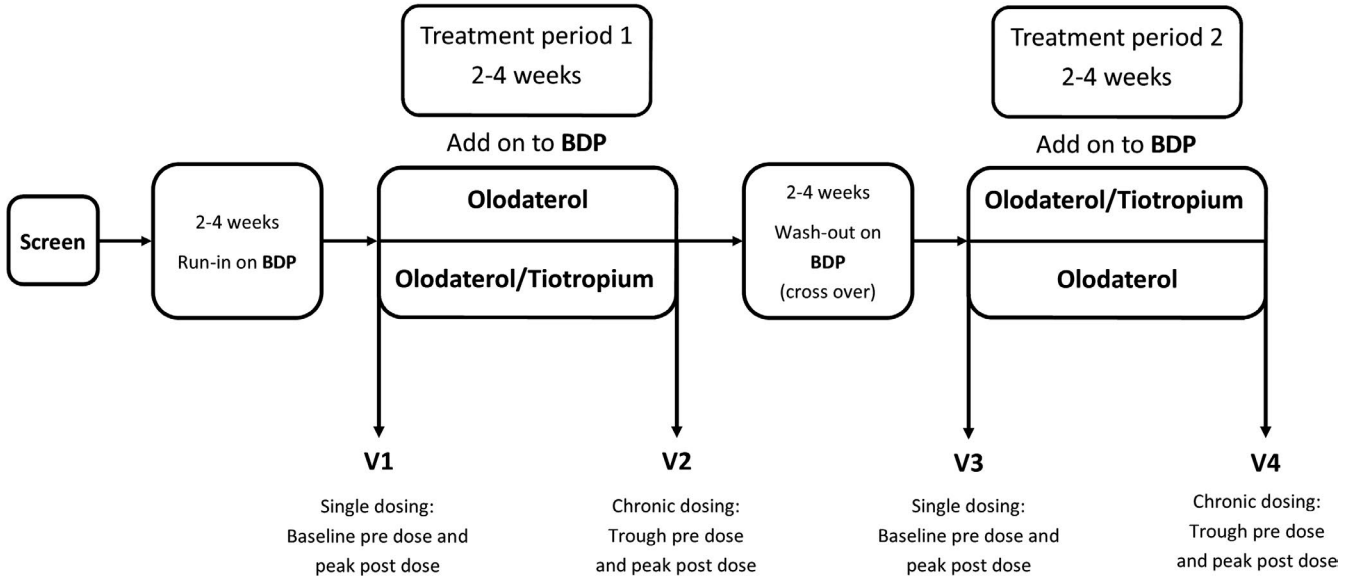

FIGURE 1 Flow chart for study visits. The median duration for treatments, run-in and washout periods was 3 weeks

were both measured at baseline before the first dose and at peak 1 hour post first dose and then at trough and peak after chronic dosing—that is trough being immediately prior to the last morning dose and peak being 1 hour post last dose. All visits were performed in the mornings (8 AM-10 AM).

Domiciliary diary data were collected for symptoms, peak flow and reliever use throughout the study.

Allergic status was defined as having at least one positive skin prick test to a panel of common aeroallergens (Diagenics Ltd, Milton Keynes, UK).

Informed consent was obtained from all patients, and ethical permission was obtained. The study was registered at clinicaltrials.gov as NCT02682862 and was approved by the East of Scotland Regional Ethics Committee (reference: 15/ES/0032).

2.1 | Statistical analysis

The study was powered on R5 as the primary end-point. Sixteen patients were required to complete per protocol to achieve 90% power in order to detect a 30% difference for the comparison between randomized treatments in R5 as change from baseline (ie OLO/TIO vs OLO), using a crossover design with alpha error of 0.05 (two tailed). The rationale was that R5 represents total airway resistance, such that if large airway resistance as R20 was unchanged, then the primary outcome would therefore reflect small airways—that is rather than powering on R5-R20 which is an artificial composite measure which encompasses two separate components of variance.

All data were first examined for normality and distribution. A comparison was made of respective baseline values after run-in and washout periods. Repeated measures analysis of variance (ANOVA) was carried out assessing for treatment and sequence effects, given the crossover design. The overall ANOVA was used to initially compare values for pooled baseline and each randomized treatment, where the overall ANOVA showed a significant overall difference a single paired t test was then applied to compare between randomized treatments, that is BDP/OLO/TIO versus BDP/OLO. In order to obviate possible confounding of the overall alpha error, no formal pairwise comparisons were made for each randomized treatment versus baseline. 95% CI for the mean difference between treatments was also derived. A *P*-value of <.05 (two tailed) was considered as being statistically significant. Statistical analysis was completed using IBM SPSS (version 22, IBM analytics, New York).

3 | RESULTS

Of seventeen patients randomized, sixteen current smokers with persistent asthma completed per protocol, 1 randomized patient was withdrawn due to failure to comply with protocol, and there were no other withdrawals post randomization (Figure 2). Participants had a mean age of 44 years, FEV1 of 84%, FEF25-75 of 47%, R5 of 158%, ACQ of 1.69, 20 pack years smoking history. The median dose of HFA-BDP during run-in was 800 μg/day. 12/16 patients had at least one positive skin prick test with a median of 2 (IQR 2-4). The median duration for treatment, run-in and washout periods was 3 weeks.

There were no differences in any outcomes comparing respective baseline values prior to treatment with OLO vs OLO/TIO (Table 1).

There were significant overall differences for IOS values after chronic dosing at trough comparing values at baseline and after randomized treatments (Table 2) with OLO or OLO/TIO. However, we did not perform individual pairwise comparisons between each randomized treatment vs baseline to obviate confounding the overall alpha error.

For the comparison between randomized treatments, after chronic dosing IOS outcomes at trough, except for R20, were

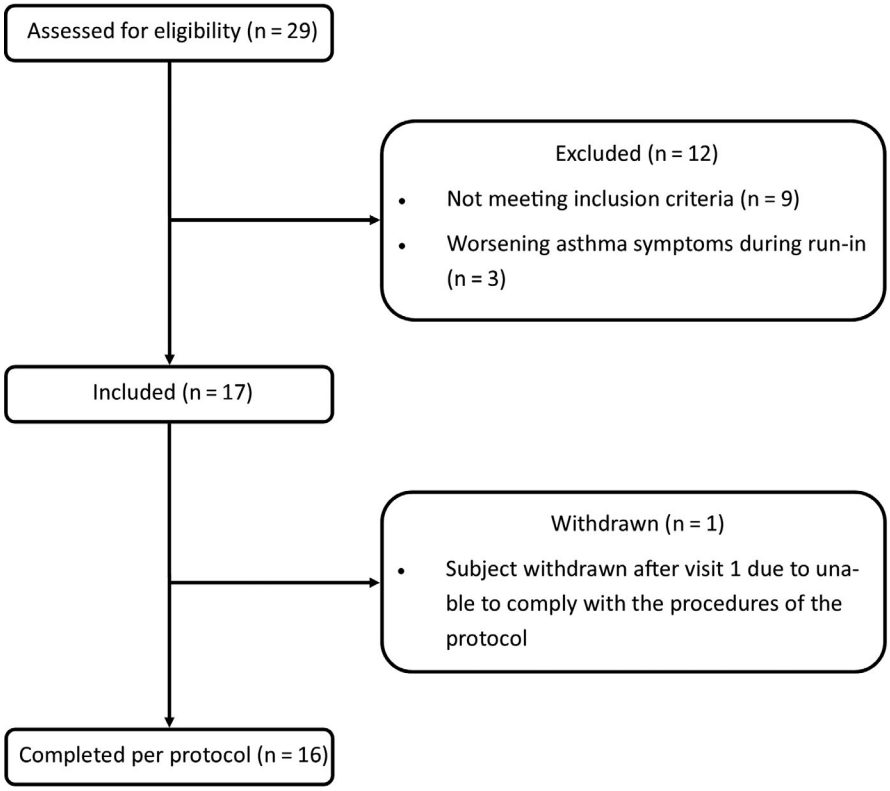

FIGURE 2 Consort diagram for participant flow

TABLE 1 Baseline values prior to randomised treatments

	PRE BDP/OLO	PRE BDP/OLO/TIO	*P*-value
FEV_1 (L)	2.42 (0.18)	2.39 (0.74)	.54
FEF_{25-75} (L/s)†	1.49 (0.17)	1.42 (0.18)	.23
FVC (L)	3.49 (0.20)	3.49 (0.21)	.98
R5 (kPa/l/s)	0.58 (0.03)	0.58 (0.04)	.82
R20 (kPa/l/s)	0.42 (0.02)	0.41 (0.02)	.55
R5-R20 (kPa/l/s)	0.16 (0.03)	0.17 (0.02)	.32
AX (kPa/l)	1.64 (0.34)	1.98 (0.35)	.19
fres (Hz)	18.70 (1.25)	20.79 (1.46)	.13
X5 (kPa/l/s)	-0.23 (0.03)	-0.25 (0.03)	.38

Note: Baseline values for lung function prior to each randomized treatment. Values are presented as mean (SEM), † Geometric mean (SEM).

P-value refers to comparison between baseline values.

Abbreviations: BDP, Beclomethasone dipropionate; OLO, Olodaterol; TIO, Tiotropium.

significantly improved with OLO/TIO compared to OLO (Table 2 and Figure 3). For the primary end-point of total airway resistance (as R5), the mean difference (95%CI) between OLO/TIO vs OLO was 0.06 (0.015-0.10) kPa/l/s, for peripheral airways resistance (as R5-R20) 0.03 (0.003-0.06) kPa/l/s, for peripheral lung reactance area (as AX) 0.38 (0.08-0.68) kPa/l, for peripheral lung reactance at 5Hz (as X5) −0.03 (−0.05 - −0.01) kPa/l/s, and for resonant frequency (as Fres) 2.28 (0.45-4.12) Hz. To estimate the minimal important difference in small airways response, we calculated from regression analysis the delta response for IOS outcomes between BDP/OLO/TIO vs BDP which corresponded to a change in ACQ of 0.5. This amounted to a 41% difference in AX and a 37% difference in R5-R20.

After chronic dosing, FEF25-75 at trough was also better with OLO/TIO vs TIO: 0.93 (0.86 - 0.95) l/s, while FEV1 at trough was not different (Table 2). There was also a small but significant difference in trough FVC between treatments (Table 2).

There were no significant differences between radnomised treatments in peak IOS and spirometry values after single or chronic dosing (Table 3).

There were significant (ANOVA $P = .007$) overall differences in mean ACQ values after chronic dosing comparing baseline (1.63) and randomized treatments: OLO (1.29) and OLO/TIO (1.03). However, there was no significant ($P = .21$) difference between treatments. The mean change from baseline in ACQ with OLO/TIO (0.59) but not OLO (0.33) exceeded the MCID of 0.5.

Domiciliary diary cards for symptoms, reliever use and peak flow showed significant overall differences between pooled baseline and randomized treatments, but there were no differences between randomized treatments (Table 4).

4 | DISCUSSION

The results of the present study revealed significantly greater improvements at trough for all IOS outcomes except for R20 when comparing ICS/LABA/LAMA to ICS/LABA in the smoking asthma phenotype. Since R20 represents changes in large airways and was no different, the changes seen in R5 and R5-R20 are therefore

TABLE 2 Trough values after chronic dosing following randomised treatments

	Pooled baseline BDP	Post BDP/OLO	Post BDP/OLO/TIO	ANOVA
FEV_1 (L)	2.40 (0.18)	2.53 (0.18)	2.60 (0.18)	<0.001
FEF_{25-75} (L/s)†	1.46 (0.17)	1.58 (0.18)	2.51 (0.17) **	<0.001
FVC (L)	3.49 (0.20)	3.59 (0.21)	3.69 (0.20)*	<0.001
R5 (kPa/l/s)	0.58 (0.03)	0.56 (0.045)	0.51 (0.40)*	0.002
R20 (kPa/l/s)	0.42 (0.02)	0.41 (0.02)	0.39 (0.02)	0.047
R5-R20 (kPa/l/s)	0.17 (0.03)	0.15 (0.03)	0.12 (0.03)*	0.007
AX (kPa/l)	1.81 (0.32)	1.54 (0.40)	1.16 (0.34)*	0.004
fres (Hz)	19.75 (1.19)	18.40 (1.54)	16.11 (1.48)*	0.001
X5 (kPa/l/s)	-0.24 (0.03)	-0.21 (0.03)	-0.19 (0.03)*	0.001

Note: Trough values for lung function after chronic dosing following treatment with BDP/OLO or BDP/OLO/TIO.

Values are presented as mean (SEM), † Geometric mean (SEM).

Repeated measures ANOVA *P* value for overall comparison between baseline and following randomized treatments.

Abbreviations: BDP, Beclomethasone dipropionate; OLO, Olodaterol; TIO, Tiotropium.

*Denotes significant difference ($P < .05$), **($P < .001$) between for comparison between OLO vs OLO/TIO after chronic dosing at trough.

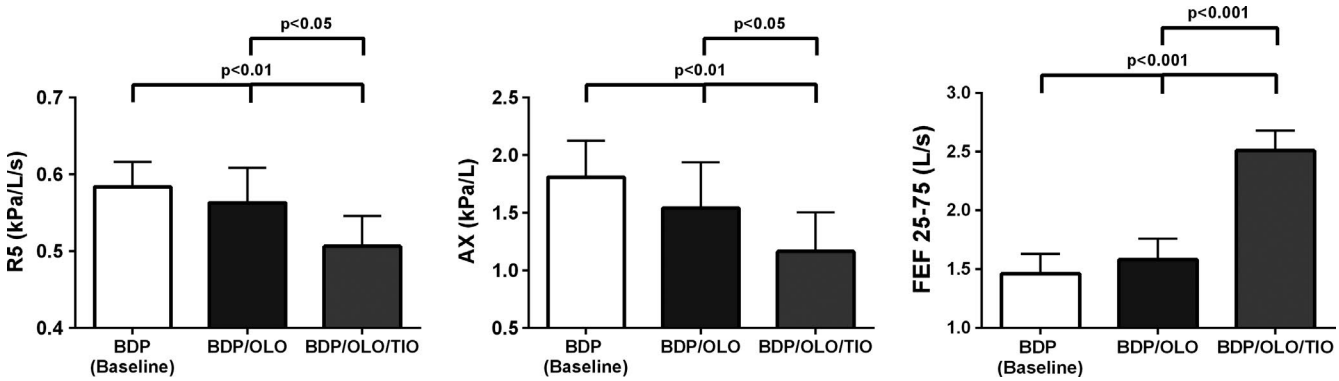

FIGURE 3 Effects of randomized treatments on trough lung function measurements after chronic dosing with either olodaterol (OLO) or olodaterol/tiotropium (OLO/TIO) added to HFA-BDP (Clenil). *P*-values are depicted for overall repeated measures ANOVA comparing baseline vs randomized treatment and also for the comparison between randomized treatments at trough after chronic dosing—that is for BDP/OLO/TIO vs BDP/OLO. Values are shown as means and SEM

indicative of effects occurring in small airways.[17] Our findings suggest that inhaled triple therapy was accompanied by attenuation of small airways dysfunction for both resistance and compliance. The observation of changes in IOS measurements at trough is clinically relevant since this coincides with the night-time period when the airways are most vulnerable to bronchoconstrictor stimuli prior to the next morning dose. The lack of any difference between randomized treatments for peak IOS response can be explained by the effect on airway caliber with OLO being maximal in terms there being no further room for improvement with TIO. Presumably, the superiority at trough but not peak for IOS outcomes with ICS/LABA/LAMA over ICS/LABA is due to a longer duration of action in small airways with TIO which is evident at the end of the 24 hours dosing interval despite there being no difference in FEV1.[24] Whether or not such superiority for trough IOS effects with triple therapy translates into reduced exacerbations in current smokers warrants further study over the longer term.In patients with uncontrolled asthma who were not current smokers, the use of medium and high dose extrafine beclometasone/formoterol/glycopyrronium (as single triple) versus beclometasone/formoterol over 52 weeks resulted in a 57-73 mL improvement in trough FEV1 along with a 12%-15% reduction in exacerbations and no difference in ACQ.[23]

Our results showed that FEF25-75 but not FEV1 was also sensitive in detecting improved response at trough comparing randomized treatments. FEF25-75 is thought to reflect volume dependent closure in small airways.[9] Hence, we took great care to ensure that patients always breathed out all the way to residual volume, along with close inspection of the expiratory flow volume loop with each measurement. In this regard, we have previously reported that abnormal values of FEF25-75 and R5-R20 are equally predictive of oral corticosteroid and salbutamol use over a 2-year period.[25] There was also a small but significant difference in FVC between treatments which could represent subtle changes in air trapping due to small airways disease, as has previously been shown on imaging with extrafine particle HFA-BDP.[26]

TABLE 3 Peak values post dose following single and chronic dosing with randomised treatments

		Single dose post			Chronic dose post		
	Pooled baseline BDP	BDP/OLO	BDP/OLO/TIO	ANOVA	BDP/OLO	BDP/OLO/TIO	ANOVA
FEV_1 (L)	2.40 (0.18)	2.64 (0.19)	2.65 (0.20)	<0.001	2.70 (0.19)	2.74 (0.18)	<0.001
FEF_{25-75} (L/s)†	1.46 (0.17)	1.79 (0.20)	1.78 (0.23)	<0.001	1.82 (0.21)	1.85 (0.21)	<0.001
FVC (L)	3.49 (0.20)	3.65 (0.21)	3.63 (0.21)	<0.001	3.71 (0.21)	3.77 (0.20)	<0.001
R5 (kPa/l/s)	0.58 (0.03)	0.44 (0.03)	0.43 (0.03)	<0.001	0.45 (0.04)	0.44 (0.04)	<0.001
R20 (kPa/l/s)	0.42 (0.02)	0.36 (0.02)	0.35 (0.02)	<0.001	0.36 (0.02)	0.36 (0.02)	<0.001
R5-R20 (kPa/l/s)	0.17 (0.03)	0.09 (0.02)	0.08 (0.02)	<0.001	0.09 (0.02)	0.08 (0.02)	<0.001
AX (kPa/l)	1.81 (0.32)	0.84 (0.23)	0.75 (0.21)	<0.001	0.80 (0.23)	0.70 (0.22)	<0.001
fres (Hz)	19.75 (1.19)	14.66 (1.17)	14.48 (1.15)	<0.001	14.09 (1.27)	13.69 (1.19)	<0.001
X5 (kPa/l/s)	-0.24 (0.03)	-0.17 (0.03)	-0.15 (0.02)	<0.001	-0.16 (0.02)	-0.15 (0.02)	<0.001

Note: Peak values post dose for lung function after single and chronic dosing.

Values are presented as mean (SEM), † Geometric mean (SEM).

Repeated measures ANOVA *P*-value for overall comparison between baseline and randomized treatments.

There were no significant differences between BDP/OLO/TIO vs BDP/OLO.

Abbreviations: BDP, Beclomethasone dipropionate; OLO, Olodaterol; TIO, Tiotropium.

TABLE 4 Domiciliary daird card data

	BDP	Post BDP/OLO	Post BDP/OLO/TIO	ANOVA
Symptoms am	0.71 (0.12)	0.51 (0.14)	0.39 (0.10)	0.012
Symptoms pm	0.63 (0.10)	0.31 (0.12)	0.27 (0.08)	<0.001
Reliever am (puffs/day)	1.05 (0.20)	0.55 (0.17)	0.45 (0.15)	0.009
Reliever pm (puffs/day)	0.92 (0.20)	0.55 (0.15)	0.33 (0.09)	0.009
PEF am (L/min)	369 (26)	384 (29)	385 (28)	0.018
PEF pm (L/min)	388 (31)	408 (34)	420 (31)	0.002

Note: Domiciliary diary card values are presented as means (SEM).

Repeated measures ANOVA *P*-value for overall comparison between baseline and randomized treatments. There were no significant differences between BDP/OLO/TIO vs BDP/OLO.

Abbreviations: BDP, Beclomethasone dipropionate; OLO, Olodaterol; PEF, peak expiratory flow; TIO, Tiotropium.

It is also noteworthy that the change in ACQ from baseline exceeded the minimal clinical important difference of 0.5[27] in response to ICS/LABA/LAMA but not ICS/LABA, although the difference between treatments was not significant per se. The effect of ICS/LABA/LAMA on ACQ may be clinically pertinent in the longer term as ACQ is known to be a strong predictor of future exacerbations.[28,29] Further studies will be required to confirm whether the use of single inhaler triple therapy results in reduction in long-term exacerbation risk.

Our results showed no significant difference between randomised treatments in diary card recordings of domiciliary peak flow, reliever use or symptoms scores, in turn suggesting that these measurements are relatively disconnected from the observed effects on small airways dysfunction.

We appreciate that there are potential limitations to our study which warrant consideration. The OLO and OLO/TIO inhalers were administered as open label. However, since both were delivered via the same Respimat device, we do not believe this would be an important confounder. One might also argue that the duration of treatment was relatively short at 2-4 weeks, although it was clearly sufficient to be able to detect differences in trough effects on IOS after chronic dosing. We gave both Respimat inhalers at the usual recommended dose of 2 puffs once daily, although we acknowledge that neither of these inhalers are licensed for asthma per se as add to ICS. We used the Respimat merely to allow us to have the same device for ICS containing dual and triple therapy and because a similar inhalation technique is required for Respimat and pMDI, to make it easier for patients to use. At the time of the study inception, it was not possible to deliver ICS/LABA and LAMA via the same device. It would now be feasible to compare single triple versus ICS/LABA inhalers via the same device such as Ellipta (Trelegy and Relvar Ellipta, GlaxoSmithKline, Uxbridge, UK) or pMDI (Trimbow and Fostair pMDI solution, Chiesi, Manchester, UK). The median daily dose of HFA-BDP as Clenil was 800ug; hence, it is possible that there may not have been such prominent effects of randomised treatments on IOS had the dose been higher or perhaps if we had used an extrafine HFA-BDP formulation.[30] Although we did not assess

adherence to the separate BDP and OLO/TIO inhalers, we are confident that the observed chronic dosing improvements in IOS with OLO/TIO compared to HFA-BDP alone are in keeping with patients having taken most of the prescribed doses as instructed. Indeed correct inhaler technique was reinforced at each visit. We did not perform any other small airways assessments such as multiple breath nitrogen washout, whole body plethysmography or imaging.[9] Further studies using these techniques might be helpful to validate our findings with triple therapy in the smoking asthma phenotype.

We have previously performed a study in mild to moderate non-smoking asthma patients where they took a either indacaterol or indacaterol/tiotropium once daily as add on to ICS.[31] In that study, we observed significant improvements compared to baseline on ICS alone for R5, R5-20 and AX, but no differences between randomized treatments. However, the smoking patients in the present study had worse asthma control as ACQ (0.72 vs 1.69) while R5% predicted values were similar (160% vs 158%). The better effects of LABA/LAMA occurring in asthmatic smokers are perhaps similar to what one might expect to see with an ACO phenotype, especially the response to LAMA.[13] The improvements seen with LAMA in addition to ICS/LABA may reflect the accentuated cholinergic bronchomotor tone which occurs such patients. One previous study compared the effects of adding in a single dose of TIO or placebo in nine smoking and nine non-smoking patients not all of whom were taking ICS/LABA. They found no significant difference in the acute response to TIO between groups in spirometry measurements—pointedly, they did not perform either chronic dosing or measure small airways with IOS.[32] We also duly acknowledge that smoking cessation strategies should be an integral part of the clinical management plan for asthmatics who smoke in addition to optimizing inhaler therapy.

In summary, we have shown that chronic dosing with triple therapy comprising ICS/LABA/LAMA is superior to dual therapy with ICS/LABA for effects on trough small airway outcomes in asthma patients who smoke. Further studies are warranted in this phenotype to evaluate whether such effects on small airways function translate into a reduced exacerbation risk when using closed single triple inhalers.

ACKNOWLEDGEMENTS

Dr Jabbal and Dr Lipworth contributed to the conception and design of the work, acquisition, analysis, interpretation of data and drafting as well as critically revising the content of the final approved version of manuscript. Dr Kuo contributed to acquisition, analysis, interpretation of data and drafting as well as critically revising the content of the final approved version of manuscript. Dr Jabbal, Dr Kuo and Dr Lipworth are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors are grateful for the particular expertise of Ashley Morrison, Kara Robertson and Deirdre Raeside in executing the study and to the patients who kindly volunteered to take part in the study. We acknowledge the financial support of NHS Research Scotland (NRS) through the NRS Primary Care Network.

CONFLICT OF INTEREST

Dr Jabbal reports personal fees and non-financial support from Chiesi Pharma, Pfizer, AstraZeneca and Mylan, non-financial support and other from Napp, non-financial support from Teva and personal fees from Boehringer Ingelheim, outside the submitted work. Dr Kuo reports personal fees from Pfizer, AstraZeneca and Chiesi, outside the submitted work. Dr Lipworth reports grants and personal fees from Boehringer Ingelheim and Mylan, grants, personal fees and non-financial support from Chiesi and AstraZeneca, personal fees from Sanofi-Regeneron and Vectura, Novartis, Lupin, personal fees and non-financial support from Teva, outside the submitted work.

AUTHOR CONTRIBUTION

Dr Jabbal and Dr Lipworth contributed to the conception and design of the work, acquisition, analysis, interpretation of data and drafting as well as critically revising the content of the final approved version of manuscript. Dr Kuo contributed to acquisition, analysis, interpretation of data and drafting as well as critically revising the content of the final approved version of manuscript. Dr Jabbal, Dr Kuo and Dr Lipworth are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be available from the corresponding author upon reasonable request up to 24 months following article publication.

ORCID

Sunny Jabbal https://orcid.org/0000-0002-9604-9807
Chris RuiWen Kuo https://orcid.org/0000-0001-5954-6620
Brian Lipworth https://orcid.org/0000-0002-8140-2014

REFERENCES

1. Chatkin JM, Dullius CR. The management of asthmatic smokers. *Asthma Res Pract*. 2016;2:10.
2. Kim YK, Kim SH, Tak YJ, et al. High prevalence of current asthma and active smoking effect among the elderly. *Clin Exp Allergy*. 2002;32:1706-1712.
3. Cerveri I, Cazzoletti L, Corsico AG, et al. The impact of cigarette smoking on asthma: a population-based international cohort study. *Int Arch Allergy Immunol*. 2012;158:175-183.
4. Jimenez-Ruiz CA, Andreas S, Lewis KE, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. *Eur Respir J*. 2015;46:61-79.
5. Clearie KL, McKinlay L, Williamson PA, Lipworth BJ. Fluticasone/Salmeterol combination confers benefits in people with asthma who smoke. *Chest*. 2012;141:330-338.
6. Willemse BW, ten Hacken NH, Rutgers B, et al. Smoking cessation improves both direct and indirect airway hyperresponsiveness in COPD. *Eur Respir J*. 2004;24:391-396.

7. Chalmers GW, Macleod KJ, Little SA, et al. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax*. 2002;57:226-230.
8. Tomlinson JE, McMahon AD, Chaudhuri R, et al. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax*. 2005;60:282-287.
9. Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. *Lancet Respir Med*. 2014;2:497-506.
10. Anderson WJ, Zajda E, Lipworth BJ. Are we overlooking persistent small airways dysfunction in community-managed asthma? *Ann Allergy Asthma Immunol*. 2012;109:185-189.e2.
11. Postma DS, Brightling C, Baldi S, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. *Lancet Respir Med*. 2019;7(5):402-416.
12. Crim C, Celli B, Edwards LD, et al. Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results. *Respir Med*. 2011;105:1069-1078.
13. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *N Engl J Med*. 2015;373:1241-1249.
14. Jetmalani K, Thamrin C, Farah CS, et al. Peripheral airway dysfunction and relationship with symptoms in smokers with preserved spirometry. *Respirology*. 2018;23:512-518.
15. Galant SP, Komarow HD, Shin HW, Siddiqui S, Lipworth BJ. The case for impulse oscillometry in the management of asthma in children and adults. *Ann Allergy Asthma Immunol*. 2017;118:664-671.
16. Lipworth BJ, Jabbal S. What can we learn about COPD from impulse oscillometry? *Respir Med*. 2018;139:106-109.
17. Foy BH, Soares M, Bordas R, et al. Lung computational models and the role of the small airways in asthma. *Am J Respir Crit Care Med*. 2019;200(8):982-991.
18. Jabbal S, Manoharan A, Lipworth J, Lipworth B. Utility of impulse oscillometry in patients with moderate to severe persistent asthma. *J Allergy Clin Immunol*. 2016;138:601-603.
19. Shi Y, Aledia AS, Tatavoosian AV, et al. Relating small airways to asthma control by using impulse oscillometry in children. *J Allergy Clin Immunol*. 2012;129:671-678.
20. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev*. 2016;CD011721.
21. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367:1198-1207.
22. Lipworth B, Kuo CR, Jabbal S. Current appraisal of single inhaler triple therapy in COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3003-3009.
23. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet*. 2019;394(10210):1737–1749.
24. Beeh KM, Westerman J, Kirsten AM, et al. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2015;32:53-59.
25. Manoharan A, Anderson WJ, Lipworth J, Ibrahim I, Lipworth BJ. Small airway dysfunction is associated with poorer asthma control. *Eur Respir J*. 2014;44:1353-1355.
26. Goldin JG, Tashkin DP, Kleerup EC, et al. Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol*. 1999;104:S258-S267.
27. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99:553-558.
28. Meltzer EO, Busse WW, Wenzel SE, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol*. 2011;127:167-172.
29. Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol*. 2010;125(3):600-608, 08 e1-08 e6.
30. Yamaguchi M, Niimi A, Ueda T, et al. Effect of inhaled corticosteroids on small airways in asthma: investigation using impulse oscillometry. *Pulm Pharmacol Ther*. 2009;22:326-332.
31. Jabbal S, Manoharan A, Lipworth BJ. Bronchoprotective tolerance with indacaterol is not modified by concomitant tiotropium in persistent asthma. *Clin Exp Allergy*. 2017;47:1239-1245.
32. Yoshida M, Kaneko Y, Ishimatsu A, et al. Effects of tiotropium on lung function in current smokers and never smokers with bronchial asthma. *Pulm Pharmacol Ther*. 2017;42:7-12.

How to cite this article: Jabbal S, Kuo CR, Lipworth B. Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics. *Clin Exp Allergy*. 2020;00:1–8. https://doi.org/10.1111/cea.13702