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Early View

Research letter

Extrafine triple therapy in patients with asthma and persistent airflow limitation

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Extrafine triple therapy in patients with asthma and persistent airflow limitation

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Running head

Triple therapy and persistent airflow limitation

Key words

Muscarinic antagonists; Adrenergic beta-2 receptor agonists; Glucocorticoids; Cohort analysis

Take-home message

These *post-hoc* analyses suggest that extrafine triple therapy with beclometasone dipropionate, formoterol fumarate and glycopyrronium may be particularly beneficial in the phenotype of patients with asthma and persistent airflow limitation.

To the Editor:

The addition of a long-acting muscarinic antagonist (LAMA) is a recognised treatment option for patients whose asthma is uncontrolled with an inhaled corticosteroid (ICS) plus long-acting β_2-agonist (LABA) combination [1]. The data supporting this recommendation were provided from studies in which the LAMA tiotropium was added to ICS/LABA combinations using separate inhalers [2, 3]. The use of separate inhalers, most often of different design, with contrasting instructions for use and dosing regimens is not only inconvenient for patients and healthcare providers who provide instruction on correct inhaler use, but can negatively impact treatment adherence and persistence – and therefore outcomes [4–7].

A single-inhaler triple therapy containing an extrafine formulation of the ICS beclometasone dipropionate (BDP), the LABA formoterol fumarate (FF) and the LAMA glycopyrronium (G) has been evaluated in two Phase 3 asthma trials – TRIMARAN and TRIGGER. These were double-blind 52-week studies that compared the efficacy and safety of BDP/FF/G with that of BDP/FF in patients with uncontrolled asthma, with TRIGGER including a third arm in which patients received open-label BDP/FF + tiotropium [8]. The design of these studies was similar, with the main difference being that TRIMARAN used a medium ICS dose (BDP/FF/G 100/6/10 µg and BDP/FF 100/6 µg, both two inhalations twice daily [BID]), whereas TRIGGER used a high ICS dose (200/6/10 µg and 200/6 µg, respectively, two inhalations BID, with patients in the third arm receiving BDP/FF 200/6 µg two inhalations BID + tiotropium 2.5 µg two inhalations once daily via Respimat). The co-primary endpoints were change from baseline in pre-dose forced expiratory volume in 1 second (FEV_1) at Week 26, and the rate of moderate-to-severe exacerbations over 52 weeks in each study. Key secondary endpoints were change from baseline in peak FEV_1 at Week 26 and in average morning peak expiratory flow (PEF) over the first 26 weeks of treatment in each study, and the rate of severe exacerbations using data pooled from the two studies. Severe exacerbations were defined as asthma worsening requiring treatment with systemic corticosteroids for at least three days, whereas moderate exacerbations were episodes of

asthma worsening that were self-managed, defined in accordance with an American Thoracic Society/European Respiratory Society joint statement [9].

Both TRIMARAN and TRIGGER recruited populations with uncontrolled asthma, who had pre-bronchodilator FEV_1 <80% predicted normal, but no limitation on post bronchodilator FEV_1 or ratio of FEV_1 to forced vital capacity (FVC). In contrast, previous asthma studies evaluating the efficacy of tiotropium added to ICS/LABA limited recruitment to patients with post-bronchodilator FEV_1 ≤80% predicted and FEV_1/FVC ratio ≤0.7 [10], a spirometric condition that the authors described as 'persistent airflow limitation' (PAL) since these were patients with airflow obstruction that failed to normalise after bronchodilation. Moreover, a lower FEV_1/FVC ratio has been shown to predict greater response to the LAMA tiotropium than to the LABA salmeterol [11]. We therefore decided to conduct *post-hoc* analyses of the data from TRIMARAN and TRIGGER to evaluate the effect of BDP/FF/G vs BDP/FF on lung function and exacerbations in the subset of patients with PAL, which we also defined as post-bronchodilator FEV_1 ≤80% predicted normal and FEV_1/FVC ≤0.7. Importantly, both TRIMARAN and TRIGGER excluded any patient with a diagnosis of chronic obstructive pulmonary disease (COPD) or who was a current smoker or an ex-smoker with a smoking history ≥10 pack-years [8]. For these *post-hoc* analyses, the co-primary and key secondary endpoints of each study are reported, together with times to first exacerbation. Severe exacerbations were analysed only in the pooled population, given the low occurrence of these events.

The FEV_1 and PEF endpoints were analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction and country as fixed effects, and baseline value and baseline by visit interaction as covariates (visit effect being replaced by inter-visit period effect for PEF). The number of asthma exacerbations over the 52-week treatment period was analysed using a negative binomial model including treatment, country and number of exacerbations in the previous year as fixed effects, and log-time on study as offset. Times to first exacerbation were analysed using a Cox

proportional hazards model including treatment, country and number of exacerbations in the previous year as factors.

Overall, 1149 patients were included in the intention-to-treat (ITT) population in TRIMARAN, 658 (57.3%) of whom met the PAL definition. In TRIGGER, 1429 patients were included in the ITT population, with 880 (61.6%) meeting the PAL definition. With the exception of lung function, baseline demographics and disease characteristics were similar in the overall population and the PAL subset for each treatment group (including age and smoking history).

For the three spirometry-based endpoints, BDP/FF/G consistently provided statistically superior efficacy to BDP/FF, with numerically greater efficacy in the PAL subset than in the overall population in both studies (Figure 1A). In TRIGGER, there were no statistically significant differences between BDP/FF/G and BDP/FF + tiotropium for the two FEV_1 endpoints, either overall or in the PAL subset; the difference for the PEF endpoint was not significant in the overall population, but there was a 7.4 L/min improvement for BDP/FF/G vs BDP/FF + tiotropium in the PAL subset ($p<0.05$). In TRIMARAN, BDP/FF/G reduced the rate of moderate-to-severe exacerbations vs BDP/FF by 15.4% in the overall population ($p=0.033$), and by 15.2% in the PAL subset ($p=0.106$; Figure 1B), with the time to first exacerbation prolonged by BDP/FF/G compared with BDP/FF both overall (hazard ratio [HR] 0.84 [95% CI 0.73 to 0.98]; $p=0.022$) and in the PAL subset (0.82 [0.68 to 1.00]; $p=0.048$). In TRIGGER, the reductions in moderate-to-severe exacerbations were 12.0% ($p=0.110$) overall, and 25.9% ($p=0.002$) in the PAL subset (Figure 1B), with the time to first exacerbation again prolonged by BDP/FF/G vs BDP/FF both overall (HR 0.80 [0.69 to 0.93]; $p=0.004$) and in the PAL subset (HR 0.65 [0.54 to 0.78]; $p<0.001$), and no differences between BDP/FF/G and BDP/FF + tiotropium. For severe exacerbations in the pooled population, the reductions were 23.0% ($p=0.008$) overall and 33.5% ($p<0.001$) in the PAL subset (Figure 1C), with the time to first exacerbation prolonged in both analyses (overall: HR 0.79 [0.66 to 0.95]; p=0·011; PAL subset: 0.70 [0.56 to 0.89]; $p=0.003$).

Previously published results from TRIMARAN and TRIGGER have shown extrafine BDP/FF/G to be effective in improving lung function and reducing the occurrence of moderate and severe exacerbations in a population of adult patients with asthma that was uncontrolled with a medium-to-high dose of an ICS plus a LABA [8]. The current *post-hoc* analyses were conducted in a population that can be easily identified through standard spirometry, and who did not otherwise differ from the overall population, in terms of age or smoking history – and importantly patients with a diagnosis of COPD were excluded. The results suggest that this extrafine triple therapy combination may be particularly beneficial in the phenotype of patients with asthma and persistent airflow limitation who have suboptimal control despite ICS/LABA therapy.

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Conflicts of interest

DS reports personal fees from Chiesi during the conduct of the studies. Outside the submitted work, he reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Therevance, and Verona.

JCV reports personal fees from Chiesi during the conduct of the studies. In the past JCV has lectured and received honoraria from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sanofi/Regeneron, Sandoz-Hexal, Stallergens, TEVA, UCB/Schwarz-Pharma, Zydus/Cadila and possibly others, and participated in advisory boards and received honoraria from Avontec, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, MEDA, MSD, Mundipharma, Novartis, Paul-Ehrlich Institut, Regeneron, Revotar, Roche, Sanofi-Aventis, Sanofi/Regeneron, Sandoz-Hexal, TEVA, UCB/Schwarz-Pharma and possibly others, and received funding for research from Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GSK, and MSD, and has advised the Bemeinsame Bundesausschuss (GBA).

GWC reports personal fees from A. Menarini, Alk-Abello, Allergy Therapeutics, AstraZeneca-Medimmune, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, Glaxo Smith Kline, Hal Allergy, Merck Sharp & Dome, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi Genzyme/Regeneron, Stallergenes-Greer, Uriach Pharma, Teva, Valeas, ViforPharma, all outside the submitted work.

AV and MK are employees of Chiesi, the sponsor of the studies.

GG is an employee of Chiesi USA, Inc.

AP reports grants, personal fees, non-financial support and payment for advisory board membership, consultancy, payment for lectures, grants for research, and travel expenses reimbursement from Chiesi, Astrazeneca, GlaxoSmithKline, Boehringer Ingelheim, Mundipharma and TEVA, and personal fees and non-financial support from Menarini, Novartis, Zambon and Sanofi, all outside the submitted work.

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Figure legend

Figure 1. A) BDP/FF/G vs BDP/FF differences in change from baseline in pre-dose and peak FEV_1 at Week 26 and in average morning PEF over the first 26 weeks (intention-to-treat population). B) Annualised moderate and severe exacerbation rate (intention-to-treat population). C) Annualised severe exacerbation rate (pooled analysis, intention-to-treat population).

Footnote: Panel A: Data are adjusted mean differences with 95% confidence intervals and p-values. Panels B and C: Data are adjusted exacerbation rates per patient per year and adjusted rate ratios (95% confidence interval). ITT: intention-to-treat; PAL: persistent airflow limitation; BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium; FEV_1 = forced expiratory volume in 1 second; PEF: peak expiratory flow.

A)

	TRIMARAN		TRIGGER	
	Overall (ITT) (n=1149)	**PAL subset (n=658)**	**Overall (ITT) (n=1142)**	**PAL subset (n=703)**
Pre-dose FEV_1, mL	57 (15 to 99); p=0.008	89 (38 to 140); p<0.001	73 (26 to 120); p=0.003	130 (79 to 181); p<0.001
Peak FEV_1, mL	84 (40 to 129); p<0.001	119 (64 to 175); p<0.001	105 (57 to 153); p<0.001	154 (100 to 208); p<0.001
PEF, L/min	8.5 (3.6 to 13.3); p<0.001	11.3 (5.3 to 17.2); p<0.001	7.8 (3.0 to 12.6); p=0.001	14.6 (8.8 to 20.5); p<0.001