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Early View

Research letter

BDP/formoterol MART asthma exacerbation benefit increases with blood eosinophil level

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BDP/formoterol MART asthma exacerbation benefit increases with blood eosinophil level

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Take-home message

BDP/FF MART regimen reduced the incidence of severe asthma exacerbations compared with BDP/FF maintenance therapy plus salbutamol as needed across the blood eosinophil continuum, with a trend to a greater reduction in patients with higher baseline counts.

To the editor,

A number of studies have evaluated the effectiveness of a 'Maintenance And Reliever Therapy' (MART) regimen combining in a single inhaler the rapid-acting, long-acting β_2-agonist (LABA) formoterol fumarate (FF) with an inhaled corticosteroid (ICS) in asthma [1–5]. Such a regimen is now established for the treatment of moderate-to-severe asthma in adolescents and adults in many guidelines [6, 7]. Furthermore, rescue short-acting β_2-agonists (SABAs) are no longer recommended as sole therapy even for patients with mild asthma, and an ICS/FF combination used as needed is the preferred reliever therapy [6].

A number of studies have examined the impact of a MART regimen on markers of airway inflammation, with discordant findings: In a substudy conducted by Sears *et al.* a MART regimen had a similar impact on the change from baseline in sputum eosinophil levels to conventional best practice [8], whereas in a study by Pavord *et al*. MART was less effective in reducing sputum eosinophil levels than high-dose ICS/LABA maintenance treatment, resulting in a significant difference between groups [9]. In contrast in a study by Hozawa et al. a MART regimen was more effective than maintenance ICS/LABA in suppressing airways inflammation [10]. However, these studies did not evaluate the correlation between baseline inflammatory marker levels and the relative efficacy of a MART regimen on clinical outcomes in general, and asthma exacerbations in particular.

Here we therefore investigate whether, in patients with moderate-to-severe asthma, blood eosinophils are theragnostic biomarkers for the relative efficacy of an ICS/FF MART regimen versus maintenance ICS/FF plus rescue SABA. To this aim we performed *post-hoc* analyses of a randomised controlled trial in patients with uncontrolled asthma, who had been receiving ICS (with or without LABA) for at least two months prior to study entry [3]. The study was 48 weeks in duration, and recruited 1714 adults with asthma who had at least one severe asthma exacerbation in the previous 12 months, pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% predicted, and whose asthma had been treated regularly with ICS (beclometasone equivalent ≥1000 µg/day) or ICS (beclometasone equivalent ≥500 µg/day)

plus LABA for the previous two months [3]. All patients received maintenance treatment with extrafine beclometasone dipropionate (BDP) 100 µg plus FF 6 µg, one inhalation twice daily via pressurised metered dose inhaler (pMDI), for the duration of the study, including a two-week run-in period. At the end of the run-in period patients whose asthma was not fully controlled (at least one of the following: use of rescue medication more than twice a week; any limitation of activities; any nocturnal symptoms or awakenings; daytime symptoms more than twice a week; or FEV_1 <80% predicted) were randomised equally (1:1) to use as rescue medication either the same extrafine BDP/FF pMDI (i.e., MART regimen) or salbutamol (the BDP/FF+salbutamol group), both one inhalation as needed up to a maximum of six extra inhalations per day. The occurrence of a severe exacerbation was defined as an asthma deterioration resulting in admission to hospital or an emergency department visit, or requiring systemic steroids for at least three days. All patients provided written informed consent prior to any study-related procedure, and the study was registered with ClinicalTrials.gov (NCT00861926). In the overall analyses, the MART regimen significantly increased the time to first severe asthma exacerbation compared with the BDP/FF+salbutamol group, with a 34% reduction in the annualised rate of severe exacerbations ($p<0.0001$) [3]. For the current *post-hoc* analyses, the annualised rate of severe exacerbations was compared between the two treatment groups by using a Poisson regression model with number of severe asthma exacerbations as dependent variable, treatment, and country as factors, and with log-time on study as offset. We conducted two sets of analyses. First, patients were grouped by baseline blood eosinophil count into three categories: <150, 150–300 and >300 cells/µL (assessed at the end of the two-week run-in period). The second set of analyses was performed across the blood eosinophil continuum.

When analysed by blood eosinophil category, in the BDP/FF+salbutamol group the percentage of patients with at least one severe exacerbation and the rate of severe exacerbations were both highest in patients with eosinophils >300 cells/µL, but were similar in the other two eosinophil categories (Figure 1a and b). In contrast, in patients receiving the

MART regimen, severe exacerbation percentages and rates were similar in all three eosinophil categories, such that the risk reduction versus BDP/FF+salbutamol was greatest in the >300 cells/µL category (a significant 45.9% risk reduction: rate ratio 0.541 [95% CI 0.397, 0.738]; p<0.001), followed by the 150–300 cells/µL category (a significant 29.5% risk reduction; 0.705 [0.506, 0.983]; p=0.039), although when tested for an interaction between eosinophil count and treatment, the p value was not significant (p=0.191). When analysed across the blood eosinophil continuum, as with the categorical analysis, there was a trend to increasing severe exacerbation rate with increasing eosinophil counts in the BDP/FF+salbutamol group, whereas with the MART regimen the rates were similar regardless of eosinophil count (Figure 1c). Consequently, there was a trend to increasing efficacy with increasing eosinophil levels, although the MART regimen had a greater effect on exacerbations than the BDP/FF+salbutamol group across the entire blood eosinophil continuum (Figure 1d). When the interaction between eosinophil count and treatment was tested across the full continuum (therefore using all information from the data), this approached statistical significance (p=0.083) despite the study being underpowered for this type of analysis. Use of rescue medication was similar in the two treatment groups regardless of eosinophil category (adjusted mean reductions from baseline in reliever use at Week 47–48 of: eosinophils <150 cells/µl, 0.29 and 0.30 inhalations per day; 150–300 cells/µL, 0.25 and 0.25 inhalations per day; >300 cells/µL, 0.31 and 0.25 inhalations per day with the MART regimen and BDP/FF+salbutamol, respectively).

The results for the BDP/FF MART regimen in our study are consistent with those of a previous *post-hoc* analysis of the NovelSTART study, which recruited patients who had been using SABA as sole therapy for asthma, and randomised them to continue salbutamol alone as needed, to receive budesonide/FF (BUD/FF) as needed, or to receive BUD maintenance therapy plus salbutamol as needed [11]. In that *post-hoc* analysis, patients were grouped by screening blood eosinophil counts in similar categories to those we used (<150, 150–<300 and ≥300 cells/µL): For the group receiving BUD/FF as needed the incidence of severe

exacerbations was similar across blood eosinophil categories [12]. Furthermore, the relative benefit of ICS-based rescue therapy in the two studies (i.e., BDP/FF MART regimen vs BDP/FF+salbutamol in our analyses and BUD/FF as needed vs salbutamol as needed in NovelSTART) increased with increasing blood eosinophil category. The two studies together thus emphasise the importance of ICS-based rescue therapy regardless of background therapy.

Overall, therefore, BDP/FF MART reduced the incidence of severe asthma exacerbations compared with BDP/FF maintenance therapy plus salbutamol as needed across the blood eosinophil continuum and there was a trend to greater reduction of severe exacerbations in patients with higher baseline eosinophil counts.

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Conflicts of interest

GB reports honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva; he is a member of advisory boards for Amgen, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron and Teva. All of these declarations are outside the submitted work.

GN, LS and DG are employees of Chiesi, the sponsor of the study.

AP reports payment for advisory board membership, consultancy, and lectures, grants for research, and travel expenses reimbursement from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, and TEVA, payment for advisory board membership, consultancy, and lectures, and travel expenses reimbursement from Mundipharma, Zambon, Novartis, and Sanofi/Regeneron, grants for research, payment for lectures, and travel expenses reimbursement from Menarini, payment for advisory board membership and consultancy, and travel expenses reimbursement from Roche, grants for research from Fondazione Maugeri and Fondazione Chiesi, and payment for consultancy from Edmondpharma, all outside the submitted work.

References

1. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekström T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005; 171: 129–136.
2. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006; 368: 744–753.
3. Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, Fabbri LM, Rabe KF. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med 2013; 1: 23–31.
4. Rabe KF, Pizzichini E, Ställberg B, Romero S, Balanzat AM, Atienza T, Lier PA, Jorup C. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest 2006; 129: 246–256.
5. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, Michael White C, Lazarus SC, Blake K V., Lang JE, Baker WL. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma a systematic review and meta-analysis. JAMA 2018; 319: 1485–1496.
6. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW-S, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet L-P. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J 2019; 53: 1901046.
7. Cloutier MM, Dixon AE, Krishnan JA, Lemanske Jr RF, Pace W, Schatz M. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA 2020; 324: 2301–2317.
8. Sears MR, Boulet LP, Laviolette M, Fitzgerald JM, Bai TR, Kaplan A, Smiljanic-Georgijev N, Lee JSM. Budesonide/formoterol maintenance and reliever therapy: Impact on airway inflammation in asthma. Eur Respir J 2008; 31: 982–989.
9. Pavord ID, Jeffery PK, Qiu Y, Zhu J, Parker D, Carlsheimer Å, Naya I, Barnes NC. Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol. J Allergy Clin Immunol 2009; 123.
10. Hozawa S, Terada M, Hozawa M. Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step-up from inhaled corticosteroid monotherapy. Pulm Pharmacol Ther 2014; 27: 190–196.
11. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Pavord ID, Williams M, Weatherall M. Controlled trial of budesonide–formoterol as needed for mild asthma. N Engl J Med 2019; 380: 2020–2030.
12. Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Williams M, Weatherall M, Beasley R, Corin A, Helm C, Poudel B, Sheahan D, Sheahan P, Bennett M, Chang C, Ellis H, Hancox B, Hopping S, Tuffery C, Ramsahai JM, Simpson J, Wark P, Aliani M, Genco M, Capozzolo A, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. Lancet Respir Med 2020; 8: 671–680.

Figure legend

Figure 1. Severe asthma exacerbations: a) Percentage of patients with at least one exacerbation by baseline blood eosinophil category; b) Mean annualised rate and treatment contrasts by baseline blood eosinophil category; c) Mean annualised rate and treatment contrasts across baseline blood eosinophil continuum; d) Adjusted severe exacerbation rate ratio BDP/FF MART regimen vs BDP/FF maintenance plus salbutamol as needed across baseline eosinophil continuum.

BDP, beclometasone dipropionate; FF, formoterol fumarate; MART, Maintenance And Reliever Therapy; RR, risk reduction.