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Early View

Research letter

Budesonide-formoterol reliever therapy in intermittent *versus* mild persistent asthma

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Budesonide-formoterol reliever therapy in intermittent *vs* mild persistent asthma

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Take-Home message

These *post-hoc* analyses of NovelSTART provide the first evidence that the exacerbation risk reduction with budesonide-formoterol reliever therapy vs salbutamol reliever therapy is similar in adults with intermittent and mild persistent asthma.

Running title

Budesonide-formoterol: intermittent & mild asthma

Keywords

asthma, intermittent, exacerbations, control

To the Editor,

Traditional asthma maintenance therapy in adults and adolescents comprises inhaled corticosteroids (ICS), with a long-acting β_2-agonist (LABA) added if ICS monotherapy provides insufficient control [1, 2]. For patients with symptoms ≤2/week (so-called "intermittent" asthma [2]) who may represent around one-third of the asthma population [3], many guidelines still recommend short-acting β_2-agonist (SABA) rescue medication alone [2, 4]. However, SABA-only treatment is still associated with severe exacerbations [5], the incidence of which is almost halved with low-dose maintenance ICS in intermittent asthma [6], but adherence is poor [7, 8]. Since 2019, the Global Initiative for Asthma (GINA) strategy document has advised against SABA monotherapy, even in those with symptoms <2/month [9, 10]. Instead, ICS therapy is now recommended whenever rescue medication is taken, either as combined ICS-formoterol, or a separate ICS inhaler [9]. However, evidence supporting this in patients with symptoms ≤2/week is limited.

NovelSTART was a 52-week, randomised, open-label, parallel-group study in adults with mild asthma [11]. Eligible patients were using SABA as sole asthma therapy, and had either ≥1 severe exacerbation in the previous 12 months, or used SABA on ≥2 occasions in the previous four weeks. Patients were randomised to: salbutamol 100µg two inhalations as-needed; maintenance budesonide 200µg twice daily plus as-needed salbutamol; or combination budesonide-formoterol 200/6µg, one inhalation as needed. Overall, as-needed budesonide-formoterol reduced severe exacerbation risk compared with both as-needed salbutamol and maintenance budesonide plus as-needed salbutamol [11], with the effect modulated by the T2 inflammatory profile [12].

Since patients could have used SABA just twice in the previous four weeks (or not at all if they had a severe exacerbation in the previous 12 months) NovelSTART provides the first opportunity to assess the efficacy of as-needed budesonide-formoterol in intermittent asthma. We therefore conducted *post-hoc* analyses, with "intermittent asthma" defined as use of SABA-alone on ≤2 occasions/week in the four weeks before entry, and with no severe exacerbation in the previous year. The comparator subgroup had "mild persistent asthma", using SABA-alone on >2 occasions/week (but less than twice-daily) in the previous four weeks, and/or ≥1 severe exacerbation in the previous year.

In these current analyses, the main comparisons were between as-needed budesonide-formoterol and as-needed salbutamol. The associations between asthma exacerbations, randomised treatment and intermittent vs persistent subgroup were analysed by Poisson regression with an offset for time in study, severe exacerbations by logistic regression, and Asthma Control Questionnaire (ACQ)-5 by analysis of covariance with baseline value as continuous covariate (SAS v9.4). Interaction terms between treatment and subgroup evaluated differences between subgroup responses. There was no adjustment for multiple analyses.

A total of 668 participants were included, 335 (50.1%) with intermittent asthma. At baseline this subgroup had lower SABA use than the mild persistent subgroup (1.3 vs 5.6x/week), lower ACQ-5 score (0.93 vs 1.26), and similar prebronchodilator forced expiratory volume in 1 second (90.2 vs 89.4%). In

the mild persistent subgroup, 15% had a severe exacerbation in the previous 12 months. Median blood eosinophil counts were similar in the two subgroups (0.22 [interquartile range 0.13–0.32] vs 0.23 [0.15–0.40]x10^9/L) as were fractional exhaled nitric oxide levels (35 [19–67] vs 40 [21–79]ppb).

Overall, exacerbation rates/year were lower in the intermittent than the mild persistent asthma subgroup (salbutamol: 0.265 vs 0.554; maintenance budesonide: 0.120 vs 0.241; as-needed budesonide-formoterol: 0.143 vs 0.236 respectively). Rate ratios vs salbutamol were similar with no evidence that the relative effects of ICS-containing treatments differed between the two subgroups (Figure 1A, P-interaction 0.85).

Few patients had severe exacerbations in some subgroups. In the intermittent subgroup 6.1, 7.3 and 3.1% patients receiving salbutamol, maintenance budesonide and budesonide-formoterol experienced a severe exacerbation respectively, compared with 14.7, 11.8 and 4.9% in the mild persistent subgroup. Patients receiving budesonide-formoterol had a lower risk of severe exacerbations than salbutamol, with no difference between maintenance budesonide and salbutamol (Figure 1B). There was no evidence of a difference in relative treatment effects by subgroup, P-interaction 0.76.

ACQ-5 at Week 52 was consistent with greater effectiveness of the ICS-containing therapies vs salbutamol in the overall analysis, with the relative effects similar in the two subgroups, P-interaction 0.66 (Figure 1C). For as-needed salbutamol, both alone and with maintenance budesonide, mean use in the intermittent subgroup was 38.5% of that with mild persistent asthma (Figure 1D). Use of budesonide-formoterol in the intermittent subgroup was 51.4% of that with mild persistent asthma. Use of maintenance budesonide was similar in the two subgroups.

These findings help to address the evidence gap for the use of ICS-formoterol as sole reliever therapy in adults with intermittent asthma who would not qualify for any ICS treatment by some guidelines. In addition, although recommended by international guidelines [9], the evidence for ICS used according to this regimen in intermittent asthma is scarce. Given poor adherence in asthma to inhaled therapy, especially to maintenance ICS [7, 8], ICS-formoterol as needed is a more practical option for patients with symptoms ≤2/week than expecting them to use daily ICS; combining bronchodilation with anti-inflammatory therapy is a regimen that is consistent with patients' desire for symptom relief [13]. Indeed, most patients who experienced the as-needed ICS-formoterol strategy in another clinical trial preferred it to maintenance ICS plus as-needed SABA [14]. Our analyses suggest that as-needed ICS-formoterol is likely to be at least as effective as maintenance ICS in patients with intermittent asthma.

The present findings confirmed that the intermittent asthma definition identified a group that differed from mild persistent asthma in terms of baseline symptoms and severe exacerbation history. As symptom burden in this population is relatively low, the rationale for ICS or as-needed budesonide-formoterol use to reduce the population-level risk of exacerbations becomes compelling, which is also consistent with the primary outcome of the original study. Furthermore, the lower exacerbation risk and low use of salbutamol reliever in the intermittent asthma subgroup during the study demonstrated the stability of this trait. In addition, the greater reduction in severe exacerbation risk with budesonide-formoterol than that observed with maintenance budesonide, despite about half the mean dose of

budesonide overall, adds further support to the timing of ICS use being more important than total ICS dose taken in reducing severe exacerbation risk, as reported from an analysis of the related PRACTICAL study [15].

A key strength of the current analyses is that the subgroups were similar in size, as were the treatment groups within each subgroup. Limitations include that these were *post-hoc*, unpowered analyses from a single, open-label study, which therefore need to be confirmed in a prospectively designed study. In addition, the low rate of exacerbations during the study limit the conclusions that can be drawn.

In conclusion, these *post-hoc* subgroup analyses challenge the current recommendations in many guidelines, that patients with symptoms or SABA use twice a week or less should be treated only with as-needed SABA. The results show that the greater efficacy of as-needed budesonide-formoterol over as-needed salbutamol, particularly for reduction in risk of exacerbations, is similar in intermittent and mild persistent asthma without the requirement for daily treatment. Importantly, these findings provide support to the recommendations in GINA 2019 onwards for the use of as-needed low dose ICS-formoterol by patients with asthma who have infrequent symptoms, who comprise a sizeable proportion of the overall asthma population.

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Conflict of interest statement

Dr Papi reports grants and personal fees from the Medical Research Institute of New Zealand during the conduct of the study. Outside the submitted work, he reports grants, personal fees, non-financial support and other from GlaxoSmithKline, Boehringer Ingelheim, Chiesi Farmaceutici, and TEVA, grants, personal fees and non-financial support from AstraZeneca and Menarini, personal fees, non-financial support and other from Mundipharma, Zambon, Novartis, and Sanofi/Regeneron, personal fees from Roche and Edmondpharma, and grants from Fondazione Maugeri and Fondazione Chiesi.

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Dr Hancox reports personal fees from Menarini, personal fees and other from Astra Zeneca, and other from Boehringer Ingelheim during the conduct of the study.

Dr Harrison reports grants from the Medical Research Institute of New Zealand during the conduct of the study. Outside the submitted work, he reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, and personal fees from Vectura, Synairgen, and Chiesi.

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Dr Morandi reports grants from Medical Research Institute of New Zealand during the conduct of the study.

Dr Oldfield reports grants from the Health Research Council of New Zealand and from AstraZeneca during the conduct of the study.

Dr Pavord reports personal fees from AstraZeneca, Aerocrine, Almirall, Novartis, GlaxoSmithKline, Genentech, and Regeneron, speaker’s honoraria, payments for organising educational events and

sponsorship to attend scientific meetings from Teva, speaker's honoraria from Chiesi, advisory board honoraria from Sanofi, Circassia, and Knopp, and grants from the UK National Institute for Health Research, all outside the submitted work.

Dr Reddel reports grants from AstraZeneca and from the Health Research Council of New Zealand during the conduct of the study. Outside the submitted work she reports grants and personal fees from AstraZeneca, grants and personal fees from GlaxoSmithKline, and personal fees from Merck, Novartis, TEVA, Boehringer Ingelheim, and Sanofi Genzyme, outside the submitted work. Dr Reddel is Chair of the GINA Science Committee.

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Dr Weatherall has nothing to disclose.

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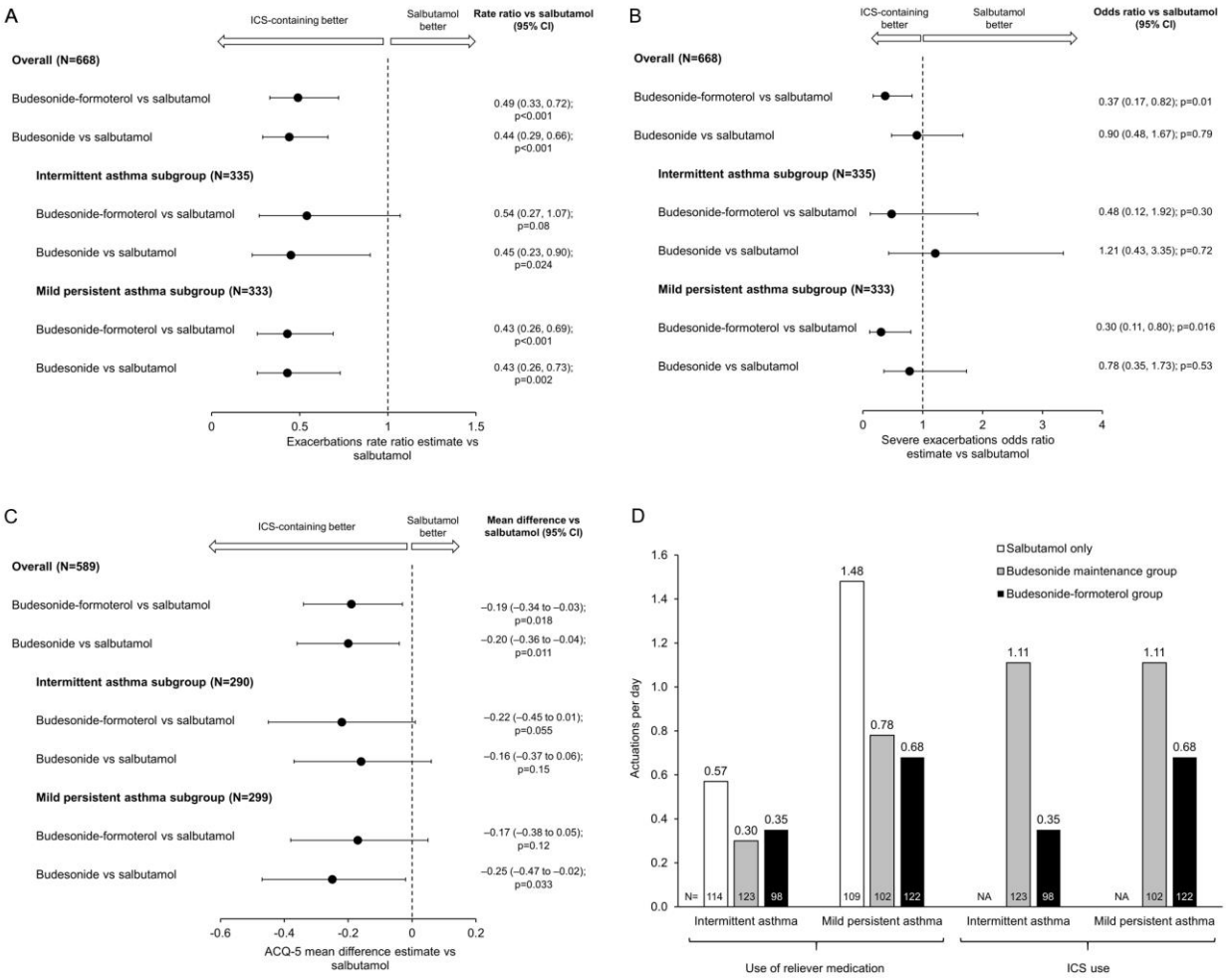
Figure legends

Figure 1. A) All exacerbations: Rate ratios for budesonide-formoterol or budesonide maintenance vs salbutamol only. B) Severe exacerbations: Odds ratios for budesonide-formoterol or budesonide maintenance vs salbutamol only. C) ACQ-5 score at Week 52: Mean differences for budesonide-formoterol or budesonide maintenance vs salbutamol only. D) Mean reliever and ICS use over the course of the trial from electronic monitoring. ACQ, Asthma Control Questionnaire; CI, confidence interval; ICS, inhaled corticosteroid.


A
ICS-containing better
Salbutamol better
Rate ratio vs salbutamol (95% CI)
Overall (N=668)
Budesonide-formoterol vs salbutamol
0.49 (0.33, 0.72); p<0.001
Budesonide vs salbutamol
0.44 (0.29, 0.66); p<0.001
Intermittent asthma subgroup (N=335)
Budesonide-formoterol vs salbutamol
0.54 (0.27, 1.07); p=0.08
Budesonide vs salbutamol
0.45 (0.23, 0.90); p=0.024
Mild persistent asthma subgroup (N=333)
Budesonide-formoterol vs salbutamol
0.43 (0.26, 0.69); p<0.001
Budesonide vs salbutamol
0.43 (0.26, 0.73); p=0.002
0
0.5
1
1.5
Exacerbations rate ratio estimate vs salbutamol
B
ICS-containing better
Salbutamol better
Odds ratio vs salbutamol (95% CI)
Overall (N=668)
Budesonide-formoterol vs salbutamol
0.37 (0.17, 0.82); p=0.01
Budesonide vs salbutamol
0.90 (0.48, 1.67); p=0.79
Intermittent asthma subgroup (N=335)
Budesonide-formoterol vs salbutamol
0.48 (0.12, 1.92); p=0.30
Budesonide vs salbutamol
1.21 (0.43, 3.35); p=0.72
Mild persistent asthma subgroup (N=333)
Budesonide-formoterol vs salbutamol
0.30 (0.11, 0.80); p=0.016
Budesonide vs salbutamol
0.78 (0.35, 1.73); p=0.53
0
1
2
3
4
Severe exacerbations odds ratio estimate vs salbutamol
C
ICS-containing better
Salbutamol better
Mean difference vs salbutamol (95% CI)
Overall (N=589)
Budesonide-formoterol vs salbutamol
−0.19 (−0.34 to −0.03); p=0.018
Budesonide vs salbutamol
−0.20 (−0.36 to −0.04); p=0.011
Intermittent asthma subgroup (N=290)
Budesonide-formoterol vs salbutamol
−0.22 (−0.45 to 0.01); p=0.055
Budesonide vs salbutamol
−0.16 (−0.37 to 0.06); p=0.15
Mild persistent asthma subgroup (N=299)
Budesonide-formoterol vs salbutamol
−0.17 (−0.38 to 0.05); p=0.12
Budesonide vs salbutamol
−0.25 (−0.47 to −0.02); p=0.033
-0.6
-0.4
-0.2
0
0.2
ACQ-5 mean difference estimate vs salbutamol
D
Salbutamol only
Budesonide maintenance group
Budesonide-formoterol group
Actuations per day
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
0.57
0.30
0.35
1.48
0.78
0.68
1.11
0.35
1.11
0.68
N=
114
123
98
109
102
122
NA
123
98
NA
102
122
Intermittent asthma
Mild persistent asthma
Intermittent asthma
Mild persistent asthma
Use of reliever medication
ICS use