Online supplement

Title

Effect of different asthma treatments on risk of cold-related exacerbations

Authors

Helen K Reddel[1], Christine Jenkins[1], Santiago Quirce[2], Malcolm R Sears[3], Eric D Bateman[4], Paul M O'Byrne[3], Marc Humbert[5], Roland Buhl[6], Tim Harrison[7], Guy G Brusselle[8], Anders Thorén[9], Ulf Sjöbring[9], Stefan Peterson[9], Ollie Östlund[9], Göran S Eriksson[9,10]

Author affiliations

[1]Clinical Management Group, Woolcock Institute of Medical Research, Sydney, Australia

[2]Department of Allergy, Hospital La Paz, Universidad Autónoma de Madrid, Madrid, Spain

[3]Michael G DeGroote School of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

[4]Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa

[5]Université Paris-Sud 11, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine-Béclère, Clamart Cedex, France

[6]Pulmonary Department, Mainz University Hospital, Mainz, Germany

[7]Nottingham Respiratory Biomedical Research Unit, City Hospital Campus, Nottingham University, Nottingham, UK

[8]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

[9]AstraZeneca Research and Development, Lund, Sweden

[10]Department of Respiratory Medicine and Allergology, University Hospital, Lund, Sweden

METHODS

This retrospective analysis included five long-term, double-blind, randomised, parallel-group clinical studies (6–12 months in duration) investigating the efficacy of budesonide/formoterol maintenance and reliever therapy (Symbicort SMART®, AstraZeneca AB, Lund, Sweden) with the following comparator therapies: higher maintenance dose budesonide plus a short-acting β_2-agonist (SABA) as needed (terbutaline [Bricanyl®], AstraZeneca, Sweden) [1, 2], same maintenance dose budesonide/formoterol (Symbicort, AstraZeneca, Lund, Sweden) plus terbutaline [1, 3] or formoterol (long-acting β_2-agonist [LABA]; Oxis®, AstraZeneca, Sweden) as needed [3] and higher maintenance dose budesonide/formoterol [4] or salmeterol/fluticasone (Seretide™, GlaxoSmithKline, Uxbridge, UK) plus terbutaline as needed [4, 5]. The original primary end point for all studies included in the pooled analysis was time to first severe exacerbation.

In the present study, for the main analysis, the efficacy of budesonide/formoterol maintenance and reliever therapy was compared with pooled efficacy data from all the fixed-dose maintenance treatments plus SABA as needed. Similar comparisons were also made between budesonide/formoterol maintenance and reliever therapy and the individual fixed-dose maintenance regimens. In the study by Rabe *et al.* [3], data from the same-dose inhaled corticosteroid (ICS)/LABA plus LABA as-needed treatment arm were excluded from the main pooled analyses (budesonide/formoterol maintenance and reliever therapy vs. all pooled comparators with SABA as needed). However, a subanalysis comparing budesonide/formoterol maintenance and reliever therapy with same-dose ICS/LABA plus SABA and plus LABA was performed.

One study excluded from this analysis was a further study by Rabe *et al.* (budesonide/formoterol maintenance and reliever therapy compared with higher maintenance dose budesonide plus SABA as needed); this study was excluded as morning peak expiratory flow was the primary variable [6], rather than time to first severe exacerbation as in the included studies.

All aforementioned drugs were administered via the Turbuhaler® (AstraZeneca, Lund, Sweden) except for salmeterol/fluticasone which was delivered via either Diskus™ [5] or Evohaler™ [4] (GlaxoSmithKline, UK). Further details on each of these studies are summarised in Table E1. The detailed methodologies of the five studies have been published in detail previously [1-5].

Written informed consent was obtained from each adult patient; for underage patients, informed consent from both the patient and his/her legal guardian was obtained.

Inclusion and exclusion criteria

Similar inclusion and exclusion criteria were applied to all studies; in general, inclusion criteria included male and female patients aged ≥ 12 years (one study 4–80 years [1]) with a diagnosis of asthma, a history of ≥ 1 asthma exacerbation in 12 months prior to study entry, use of ICS for ≥ 3 months prior to study entry, a forced expiratory volume in 1 second (FEV_1) ≥ 50% of predicted normal (pre-bronchodilator), and ≥ 12% (and, for patients aged ≥ 18 years in two studies, ≥ 200 ml [2, 3]) increase from baseline FEV_1 15 minutes after inhalation of terbutaline 1 mg. Patients with any respiratory infection affecting their asthma or using oral corticosteroids within 1 month of study entry were excluded from the studies. To be eligible for randomisation, patients had to have used ≥ 12 inhalations (or ≥ 8 in children) of as-needed medication during the last 10 days of run-in. Patients using ≥ 10 inhalations of reliever on any 1 day (or ≥ 7 for children) or with an asthma exacerbation during run-in were not randomised.

Statistical methods and stability analyses

The number of exacerbations in each season was analysed in a Poisson model for correlated observations, with factors treatment, season, treatment–season interaction, hemisphere, hemisphere–season interaction and study, with (log-transformed) observation time as an offset; in this analysis, patients resident in the tropics were not included. The model was fitted using a Generalised Estimating Equation method, estimating a correlation

coefficient for winter and summer observations within patients, and using a robust estimator for covariance. The results were checked under several different model choices. Adjustment for time on treatment, which could be confounded with seasonal variation, was attempted by including randomisation month and randomisation month–season interaction in the Poisson model. Time to exacerbation was investigated using a proportional hazard model with (time-dependent) factors treatment, season, and treatment–season interaction, stratified by study. This model, which inherently adjusts for effects of time on treatment, was fitted both for time to first exacerbation (ordinary Cox regression) and for repeated events (Anderson–Gill formulation, using a robust covariance estimator). The results were stable under all models (Table E3).

The number of exacerbations in cold periods (Days 0–14 after onset of a reported cold) and non-cold periods was analysed using a Poisson model of the same kind as for seasonal variation, with factors treatment, cold status (cold period/non-cold period), treatment–cold status interaction, geographic area (northern hemisphere, southern hemisphere or tropics), and study. The results were compared with those from a proportional hazard model with time-dependent factors treatment, cold status, and treatment–cold status interaction stratified by study. The model was fitted both for time to first exacerbation and for repeated events.

A further analysis of exacerbations during cold periods was performed using a Poisson model with factors treatment and study, with observation time (censored at 14 days) as an offset, adjusted for overdispersion, and a Cox proportional hazard model with factor treatment, stratified by study, for time from onset of first cold to first exacerbation, censored at 14 days after onset of cold. The results were stable under all models (Table E4).

References for Online Supplement

1. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom 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. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, Boulet LP, Naya IP, Hultquist C. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004; 20: 1403-1418.

3. 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.

4. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract* 2007; 61: 725-736.

5. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, Carlsheimer A. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007; 101: 2437-2446.

6. Rabe KF, Pizzichini E, Stallberg 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.

7. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2009 [cited August 2010]; Available from: www.ginasthma.com

Online supplement table E1: Summary of the five clinical trials used in this retrospective analysis

Treatment arms	Study duration, months	N	Mean ICS, µg/day (BDP equiv)*†	Reference and study code
BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS + SABA				
1. BUD/FORM maintenance + reliever (80/4.5µg BID + 80/4.5µg as needed) vs.	12	925	240 (375)	O'Byrne *et al.* [1]
BUD (320 µg BID) + terbutaline as needed		926	640 (1000)	SD-039-0735
2. BUD/FORM maintenance + reliever (2x160/4.5µg OD + 1x160/4.5µg as needed) vs.	12	947	466 (728)	Scicchitano *et al.* [2]
BUD (2 x 160 µg BID) + terbutaline as needed		943	640 (1000)	SD-039-0668
BUD/FORM maintenance and reliever therapy vs. same maintenance dose ICS/LABA + SABA				
1. BUD/FORM maintenance + reliever (80/4.5µg OD + 80/4.5µg as needed) vs.	12	925	240 (375)	O'Byrne *et al.* [1]
BUD/FORM (80/4.5 µg BID) + terbutaline as needed		909	160 (250)	SD-039-0735
2. BUD/FORM maintenance + reliever (160/4.5 µg BID + 160/4.5µg as needed) vs.	12	1113	483 (755)	Rabe *et al.* [3]
BUD/FORM (160/4.5 µg BID) + terbutaline or formoterol‡ as needed		2281	320 (500)	SD-039-0734
BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS/LABA + SABA				
1. BUD/FORM maintenance + reliever (160/4.5µg BID + 160/4.5µg as needed) vs.	6	1107	483 (755)	Kuna *et al.* [4]
BUD/FORM (320/9 µg BID) + terbutaline as needed		1105	640 (1000)	SD-039-0735
SAL/FLU (2 x 25/125 µg BID) + terbutaline as needed		1123	500 (1000)	

2. BUD/FORM maintenance + reliever (2x160/4.5 µg BID + 1x160/4.5µg as needed)	6	1154	792 (1238)	Bousquet *et al.* [5],
vs.		1155	1000 (2000)	NCT00242775
SAL/FLU (50/500 µg BID) + terbutaline as needed				

* Microgram dose of ICS is stated as prescribed regular daily dose. In patients on budesonide/formoterol maintenance and reliever therapy, the additional mean dose of ICS taken as needed as recorded in the patient diary has been added to the regular daily dose. † Mean ICS doses converted to BDP-CFC equivalents based on GINA guidelines [7]. ‡ Only data from the terbutaline as-needed arm were included in the main pooled analysis (n = 1141) (budesonide/formoterol maintenance and reliever therapy vs. all pooled comparators); data from the formoterol as-needed arm (n = 1140) were excluded in this analysis. BDP, beclomethasone dipropionate; BID, twice daily; BUD/FORM, budesonide/formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OD, once daily; SABA, short-acting β_2-agonist; SAL/FLU, salmeterol/fluticasone.

Online supplement table E2: Demographic and baseline data by treatment and geographic area

	Northern hemisphere	Southern hemisphere	Tropics
	All	All	All
A) All patients from studies with BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS + SABA			
N	2984	501	246
Male, n (%)	1356 (45)	198 (40)	75 (30)
Age, mean (range)	39.6 (4–80)	38.3 (7–79)	36.4 (12–71)
ICS, µg (range)	678 (100–2000)	744 (200–1600)	617 (250–1000)
LABA use, n (%)	1151 (39)	129 (26)	38 (15)
Asthma diagnosis, median years (range)	10 (0–71)	18 (1–71)	13 (1–69)
FEV_1, % predicted normal	72.0 (10.3)	71.3 (10.8)	70.0 (8.3)
As-needed reliever use, inhalations/day	2.09 (1.53)	2.40 (1.61)	2.72 (1.34)
Total daily symptom score, range 0–6	1.71 (0.99)	1.67 (0.84)	1.38 (1.03)
B) All patients from studies with BUD/FORM maintenance and reliever therapy vs. same maintenance dose ICS/LABA + SABA*			
N	3075	430	568
Male, n (%)	1363 (44)	161 (37)	168 (30)
Age, mean (range)	39.3 (4–89)	36.7 (5–78)	39.5 (12–82)
ICS, µg (range)	693 (160–1600)	678 (200–2000)	675 (250–1600)
LABA use, n (%)	1465 (48)	163 (38)	202 (36)
Asthma diagnosis, median years, range	8 (0–65)	15 (1–64)	14 (1–69)
FEV_1, % predicted normal	73.9 (11.3)	69.5 (11.1)	67.6 (10.7)
As-needed reliever use, inhalations/day	2.04 (1.32)	2.29 (1.24)	2.46 (1.56)
Total daily symptom score, range 0–6	1.60 (0.94)	1.81 (0.91)	1.51 (0.93)

C) All patients from studies with BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS/LABA + SABA			
N	2923	1811	891
Male, n (%)	1253 (43)	767 (42)	268 (30)
Age, mean (range)	38.9 (11–82)	36.8 (12–83)	41.3 (12–78)
ICS, µg (range)	724 (200–2400)	733 (250–3200)	752 (100–2000)
LABA use, n (%)	1602 (55)	788 (44)	397 (45)
Asthma diagnosis, median years, range	8 (0–69)	16 (1–70)	12 (1–77)
FEV_1, % predicted normal	73.0 (13.9)	72.7 (13.9)	65.9 (12.8)
As-needed reliever use, inhalations/day	2.18 (1.37)	2.50 (1.42)	2.24 (1.43)
Total daily symptom score, range 0–6	1.88 (0.95)	2.03 (0.93)	1.77 (0.94)

Pooled baseline demographic data from all patients (budesonide/formoterol maintenance and reliever therapy and comparator treatment) split by geographic location. Data are means (standard deviation) unless otherwise indicated.

* The ICS/LABA plus formoterol as-needed arm in the study by Rabe *et al.* [3] was not included in this pooled analysis, but no differences in baseline data were seen for this treatment arm. For individual demographic data for the different treatment groups, please refer to the individual publications (higher maintenance dose ICS plus SABA [1,2]; same maintenance dose ICS/LABA plus SABA [1,3]; higher maintenance dose ICS/LABA plus SABA [4,5]; budesonide/formoterol maintenance and reliever therapy [1–5].

BUD/FORM, budesonide/formoterol; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

Online supplement table E3: Analysis of number of exacerbations and time to first severe exacerbation by season* using different statistical models

	Season	
	Summer	**Winter**
Number of exacerbations, rate or ratio (95% CI); pooled data from all studies		
Basic model		
BUD/FORM maintenance and reliever therapy	0.18 (0.16–0.21)	0.26 (0.24–0.30)
Pooled fixed-dose maintenance treatments + SABA†	0.32 (0.29–0.35)	0.48 (0.44–0.52)
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA†	0.57 (0.49–0.68); *P* < 0.001	0.56 (0.49–0.64); *P* < 0.001
Extended model		
BUD/FORM maintenance and reliever therapy	0.18 (0.15–0.20)	0.25 (0.22–0.29)
Pooled fixed-dose maintenance treatments + SABA†	0.31 (0.28–0.34)	0.45 (0.41–0.50)
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA†	0.57 (0.48–0.67); *P* < 0.001	0.56 (0.49–0.64); *P* < 0.001
Time to severe exacerbation, hazard ratio (95% CI); pooled data from all studies		
Cox time-to-first		
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA†	0.67 (0.57–0.79); *P* < 0.001	0.62 (0.55–0.71); *P* < 0.001
Anderson-Gill repeated events		
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA†	0.60 (0.51–0.71); *P* < 0.001	0.57 (0.50–0.66); *P* < 0.001

*****For seasonality analyses patients resident in the tropics were not included. † The ICS/LABA plus formoterol as-needed arm in the study by Rabe *et al.* [3] was not included in these pooled analyses.

BUD/FORM, budesonide/formoterol; CI, confidence interval; SABA, short-acting β_2-agonist

Online supplement table E4: Analysis of severe exacerbations by cold status

	Cold period	Non-cold period
Cox time-to-first, hazard ratio (95% CI)		
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA*	0.65 (0.49–0.86); *P* = 0.003	0·63 (0.57–0.70); *P* < 0.001
Anderson-Gill repeated events		
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA*	0.60 (0.46–0.80); *P* < 0.001	0·59 (0.52–0.66); *P* < 0.001
Poisson regression, severe exacerbation rate (events/patient/year) after first reported cold		
BUD/FORM maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA*	0.62 (0.46–0.85); *P* = 0.0026	

Analysis of number of exacerbations by cold status (cold period/non-cold period). A cold period was defined as Days 0–14 following onset of a reported cold. * The ICS/LABA plus formoterol as-needed arm in the study by Rabe *et al.* [3] was not included in this pooled analysis. BUD/FORM, budesonide/formoterol; CI, confidence interval; SABA, short-acting β_2-agonist.

Online supplement table E5: Exacerbation rates and treatment comparisons by cold status with same maintenance dose budesonide/formoterol and different reliever medications

	Mean ICS dose (μg/day, BDP equiv)	Exacerbation rate or ratio (95% CI)	
		Cold periods*	Non-cold periods
BUD/FORM maintenance + reliever therapy	755	1.87 (1.18–2.96)	0.19 (0.15–0.23)
Same maintenance dose ICS/LABA + LABA	500	3.89 (2.64–5.73)	0.27 (0.23–0.32)
Same maintenance dose ICS/LABA + SABA	500	4.06 (2.91–5.66)	0.35 (0.30–0.41)
BUD/FORM maintenance + reliever therapy vs. same maintenance dose ICS/LABA + LABA	–	0.48 (0.27–0.87); *P* = 0.015	0.70 (0.54–0.90); *P* = 0.006
BUD/FORM maintenance + reliever therapy vs. same maintenance dose ICS/LABA + SABA	–	0.46 (0.26–0.80); *P* = 0.006	0.53 (0.42–0.68); *P* < 0.001
ICS/LABA maintenance + LABA vs. same maintenance dose ICS/LABA + SABA	–	0.96 (0.58–1.59); *P* = 0.87	0.76 (0.61–0.95); *P* = 0.018

The table shows the annualised exacerbation rate (exacerbations/year) and the rate ratio for exacerbations for budesonide/formoterol maintenance and reliever therapy versus same maintenance dose budesonide/formoterol with as-needed SABA (terbutaline) or as-needed LABA (formoterol) from the study by Rabe *et al.* [3], analysed by cold status (cold period/non-cold period) using the statistical analysis model (see Methods). * A cold period was defined as the 14 days following onset of a reported cold. Cold periods comprised an average of 2.7 weeks of the treatment period per patient. Mean ICS dose was calculated as BDP-CFC equivalent, based on GINA guidelines [7], over the whole randomised treatment period, including ICS delivered in maintenance and, where relevant, reliever therapy.

BDP, CFC-beclomethasone dipropionate; BUD/FORM, budesonide/formoterol; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

Online supplement figure E1: Exacerbation rate by month in year

[Footnote to Figure E1]

Exacerbation incidence by month in year for northern and southern hemispheres (tropics not included) for budesonide/formoterol maintenance and reliever therapy vs.: A) higher maintenance dose ICS + SABA; B) same maintenance dose ICS/LABA + SABA and C) higher maintenance dose ICS/LABA + SABA, for northern and southern hemispheres by calendar month (left), and for all pooled comparators by seasonal month (right). Seasonal months: southern hemisphere 1 = January to 12 = December; northern hemisphere 1 = July to 12 = June.

* The ICS/LABA plus formoterol as-needed arm in the study by Rabe *et al.* [3] was not included in these pooled analyses. † Note that due to the short duration (6 months) of these studies, different months show different patient populations and the number of patients under observation in the northern hemisphere varies between 2698 in October and 430 in April.

BUD/FORM, budesonide/formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

Online supplement figure E2: Reliever use associated with first reported cold, for individual treatment comparisons

[Footnote to Figure E2]

For patients reporting a cold, the figure shows mean total daily reliever use (inhalations/patient/24 hours) over days –7 to 21 from the onset of first reported cold, from all studies, for budesonide/formoterol maintenance and reliever therapy and the corresponding individual comparator regimens: (A) higher dose ICS, (B) same dose maintenance ICS/LABA, (C) higher dose maintenance ICS/LABA, each with as-needed SABA.

The dotted lines indicate the on-treatment averages across the whole study for the same groups of patients.

BUD/FORM, budesonide/formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.