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RESEARCH

Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β_2 agonist: observational matched cohort study (PATHOS)

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Abstract

Objective To investigate the occurrence of pneumonia and pneumonia related events in patients with chronic obstructive pulmonary disease (COPD) treated with two different fixed combinations of inhaled corticosteroid/long acting β_2 agonist.

Design Observational retrospective pairwise cohort study matched (1:1) for propensity score.

Setting Primary care medical records data linked to Swedish hospital, drug, and cause of death registry data for years 1999-2009.

Participants Patients with COPD diagnosed by a physician and prescriptions of either budesonide/formoterol or fluticasone/salmeterol.

Main outcome measures Yearly pneumonia event rates, admission to hospital related to pneumonia, and mortality.

Results 9893 patients were eligible for matching (2738 in the fluticasone/salmeterol group; 7155 in the budesonide/formoterol group), yielding two matched cohorts of 2734 patients each. In these patients, 2115 (39%) had at least one recorded episode of pneumonia during the study period, with 2746 episodes recorded during 19 170 patient years of follow up. Compared with budesonide/formoterol, rate of pneumonia and admission to hospital were higher in patients treated with fluticasone/salmeterol: rate ratio 1.73 (95% confidence interval 1.57 to 1.90; P<0.001) and 1.74 (1.56 to 1.94; P<0.001), respectively. The pneumonia event rate per 100 patient years for fluticasone/salmeterol versus budesonide/formoterol was 11.0 (10.4 to 11.8) versus 6.4 (6.0 to 6.9) and the rate of admission to hospital was 7.4 (6.9 to 8.0) versus 4.3 (3.9 to 4.6). The mean duration of admissions related to pneumonia was similar for both groups, but mortality related to pneumonia was higher in the fluticasone/salmeterol group (97 deaths) than in the budesonide/formoterol group (52 deaths) (hazard ratio 1.76, 1.22 to 2.53; P=0.003). All cause mortality did not differ between the treatments (1.08, 0.93 to 1.14; P=0.59).

Conclusions There is an intra-class difference between fixed combinations of inhaled corticosteroid/long acting β_2 agonist with regard to the risk of pneumonia and pneumonia related events in the treatment of patients with COPD.

Trial registration Clinical Trials.gov NCT01146392.

Tables

Table 1| Baseline characteristics in two years before first prescription for inhaled corticosteroid/long acting β2 agonist after diagnosis of COPD according to fixed combination treatment. Unmatched and pairwise (1:1) propensity matched populations are shown. Figures are means (SD) unless specified otherwise

	Unmatched				Matched			
Variable	Fluticasone/salmeterol (n=2738)	Budesonide/formoterol (n=7155)	P value	Standardised difference	Fluticasone/salmeterol (n=2734)	Budesonide/formoterol (n=2734)	P value	Standardised difference
Age (years)	67.6 (10.4)	66.7 (10.8)	<0.001	8.5	67.6 (10.4)	67.6 (10.9)	0.9	2.2
No (%) females	1459 (53)	3815 (53)	0.98	0.06	1456 (53)	1446 (53)	0.8	1.5
Post-bronchodilator FEV_1, % predicted normal*	50.5 (13.9)	55.2 (19.2)	<0.001	25.5	50.4 (19.3)	51.3 (20.2)	0.6	4.4
No (%) with any exacerbation	2105 (77)	5584 (78)	0.2	2.8	2101 (77)	2106 (77)	0.9	2.1
No (%) current smokers*	341 (48)	1337 (53)	0.03	9.2	341 (48)	397 (49)	0.7	6.9
Oral steroid prescriptions/year†	0.91 (2.37)	0.90 (2.41)	0.8	0.5	0.90 (2.31)	0.87 (2.27)	0.7	0.36
Respiratory antibiotic prescriptions/year†	0.95 (1.69)	1.02 (1.70)	0.06	4.2	0.95 (1.69)	0.95 (1.53)	0.9	0.02
Inhaled steroid prescriptions/year†	0.93 (2.04)	1.23 (2.55)	<0.001	13.1	0.93 (2.04)	0.96 (1.97)	0.5	1.0
No (%) with pneumonia diagnosis	701 (26)	1796 (25)	0.6	1.2	700 (26)	694 (25)	0.9	1.3
No of pneumonia diagnoses/year	0.15 (1.22)	0.13 (1.21)	0.5	1.7	0.15 (1.22)	0.12 (1.12)	0.4	0.49
Days in hospital because of pneumonia/year	0.14 (1.12)	0.11 (0.99)	0.2	2.7	0.14 (1.12)	0.13 (1.05)	0.8	0.71
No (%) with comorbidities:								
Asthma	1053 (38)	2300 (32)	<0.001	13.2	1052 (38)	1069 (39)	0.6	1.9
Heart failure	472 (17.2)	1169 (16.3)	0.3	2.4	470 (17.2)	483 (17.6)	0.6	0.38
Ischaemic heart disease	299 (10.9)	833 (11.6)	0.3	2.3	298 (10.9)	296 (10.8)	0.9	0.24
Diabetes	288 (11)	967 (14)	<0.001	9.3	288 (11)	283 (10)	0.8	0.95

Table 2| Pneumonia events by type for pairwise (1:1) propensity score matched populations treated with budesonide/formoterol versus fluticasone/salmeterol for COPD. All P<0.001, Poisson regression

	Event rate (95% CI)		
Measure	Fluticasone/salmeterol	Budesonide/formoterol	Treatment contrast
Diagnosis of pneumonia overall†	11.0 (10.4 to 11.8)	6.4 (6.0 to 6.9)	1.73 (1.57 to 1.90)
Admission to hospital because of pneumonia†	7.4 (6.9 to 8.0)	4.3 (3.9 to 4.6)	1.74 (1.56 to 1.94)
Diagnosis of pneumonia in primary care†	4.2 (3.9 to 4.5)	2.7 (2.5 to 2.9)	1.56 (1.39 to 1.75)
Diagnosis of pneumonia in hospital outpatient care†	1.3 (1.2 to 1.4)	0.7 (0.7 to 0.8)	1.75 (1.53 to 2.00)
Days in hospital because of pneumonia‡	52.8 (48.9 to 57.0)	29.0 (26.5 to 31.7)	1.82 (1.62 to 2.05)

*Rate ratio (95% CI) in reference to budesonide/formoterol.
†Expressed as rates per 100 patient years.
‡Expressed as hospital days per 100 patient years.

Table 3| Pneumonia rates in subpopulations of pairwise (1:1) propensity matched populations* treated with fluticasone/salmeterol v budesonide/formoterol. All P<0.001, Poisson regression

	Yearly rate		
Subpopulation	Fluticasone/salmeterol	Budesonide/formoterol	Treatment contrast†
Females	11.0	5.9	1.87 (1.64 to 2.13)
Males	11.1	7.0	1.59 (1.38 to 1.83)
Age ≤60	8.5	4.0	2.14 (1.75 to 2.62)
Age >60	12.1	7.5	1.62 (1.45 to 1.80)
Pneumonia diagnosis before index:			
Yes	22.4	12.9	1.73 (1.47 to 2.04)
No	7.6	4.3	1.76 (1.57 to 1.98)
Oral steroids/antibiotics used before index‡:			
Yes	11.7	7.3	1.61 (1.44 to 1.80)
No	9.5	4.3	2.19 (1.82 to 2.64)
Long acting bronchodilators used before index‡:			
Yes	11.4	6.6	1.73 (1.55 to 1.93)
No	9.9	5.7	1.72 (1.43 to 2.08)
Asthma diagnosis before index:			
Yes	12.4	6.6	1.88 (1.63 to 2.17)
No	9.7	6.2	1.56 (1.37 to 1.78)
Events after index:			
<1 year	13.9	8.3	1.68 (1.49 to 1.89)
<2 years	12.3	7.2	1.71 (1.53 to 1.91)
<3 years	11.8	7.3	1.63 (1.46 to 1.80)

*All event rates are expressed per 100 patient treatment years for all subpopulations based on baseline characteristics collected up to 2 years before index
†Rate ratio (95% CI) in reference to budesonide/formoterol.
‡Drug used to define COPD exacerbation history before index.