GSK Medicine: Fluticasone Propionate,Beclomethasone

Study No: WWE113663/WEUKSTV1076/EPI40470

Title: Assessment of incidence of pneumonia among COPD patients with or without exposure to inhaled steroids in the General Practice Research Database (GPRD)

Rationale: Pneumonia is a common, serious, and potentially life-threatening disease particularly among patients with risk factors for resistant pathogens and the elderly. As a comorbid condition, pneumonia has been associated with the morbidity and mortality of COPD patients Yet, very little has been reported in the published literature regarding the patterns of incidence of pneumonia in COPD.

Objectives: The objective of the study was to assess trends in the incidence of pneumonia in COPD patients using the General Practice Research Database (GPRD). Incidence trends were assessed prior to and post (1) diagnosis of COPD and (2) initiation of inhaled corticosteroids (ICS).

Indication: COPD

Study Investigators/Centers:
GSK Conducted Study

Research Methods:

Study Design: Design A was a retrospective cohort of COPD patients matched to a random sample of patients free of COPD in their medical history in the UK General Practice Research Database (GPRD). Patients were matched on year of birth, sex, general practice, and completed years of medical records up to at least a year after the index date for COPD. Design B was a retrospective cohort of COPD patients with first-time exposure to ICS post-diagnosis matched to COPD patients never exposed to ICS. Patients were matched on the same variables as in design A and additionally on COPD duration.

Data Source**:** The General Practice Research Database (GPRD) contains computerized health care information entered by General Practitioners in the UK. Over 400 General Practices have been contributing medical history data since 1987 on over 6 million patients who are broadly representative of the total population. The database contains longitudinal data on patient characteristics, medical history including records of referrals to consultants and hospitalizations, and treatment history over a period of up to 15 years. The codes used to identify COPD diagnosis in the GPRD were validated in an earlier study.

Study Population: The GPRD population of patients from 1990 to 2006 was used to identify the COPD cohort. Inclusion criteria were as follows: 1) COPD related GPRD Medical Code, (2) at least 1 Rx Code for COPD medication within 12 months after the first GPRD Medical Code between 1990-2004, (3) at least 24 months of history in the GPRD, (4) at least 12 months of history after cohort, (5) age $\geq$ 45 years at index date, and (6) without a prescription for ICS prior to COPD diagnosis. Patients were excluded according to the following criteria: (1) follow-up shorter than 24 months after the cohort entry, (2) age < 45 years at index date, (3) no COPD Rx Code recorded within 12 months after the 1st COPD GPRD Medical Code, or (4) at least 1 prescription for ICS prior to COPD diagnosis.

The non-COPD cohort was identified based on the following criteria: (1) at least 12 months of history, (2) at least 1 GPRD medical code for a condition other than COPD in the last 12 months prior to index date, (3) at least 12 months of follow-up after the index date, (4) age $\geq$ 45 years at index date, and (5) no prescription for ICS up to the end of study period. Patients with a COPD diagnosis defined by a GPRD Medical Code recorded any time in the history, < 45 years old at index date, patients with a history shorter than 24 months, and patients with at least 1 prescription for ICS were excluded from the non-COPD cohort.

Study Exposures, Outcomes: The outcomes of interest were cumulative incidence (first ever episode per person-years at risk), annual incidence (first episode in the year regardless of number of past events) and annual total incidence (all episodes in the year) of pneumonia. We adopted a minimum period of 14 days between consecutive episodes of pneumonia in our classification of re-occurrence.

The ICS exposure status of each COPD patient in the years after COPD diagnosis was used to construct the two comparative groups in design B.

Data Analysis Methods: Retrospective descriptive analyses based on matched cohorts were conducted. In the analysis

for design A, number and annual rate per 1,000 person-years in COPD and non-COPD for (a) cumulative incidence, (b) annual incidence and (c) annual total incidence levels were estimated. For design B, number and annual rate per 1,000 person-years in COPD exposed to ICS and COPD never exposed to ICS for (a) cumulative incidence, (b) annual incidence and (c) annual total incidence levels were also estimated. Rates ratios to compare the (a) cumulative incidence, (b) annual incidence and (c) annual total incidence of pneumonia in COPD/non-COPD population in design A and in COPD exposed to ICS/COPD never exposed to ICS in design B were calculated.

Two separate linear regression lines were fit to assess changes in the annual rate/ratios for the entire ten-year observation period and for the 5-year period prior to the index date. Comparison of the two slopes provided measures on annual changes in the corresponding periods. In Design B, we also used the fitted line for the prior-ICS initiation period to obtain expected annual rate ratios for the post initiation period.

Limitations:

Study Results: A total of 10,918 incident physician-diagnosed patients with COPD where matched to an equal number of patients free of COPD between 1990 and 2006. Two distinctions stood out between the two cohorts, namely, there were more current smokers (40%) and fewer non-smokers (13%) among the COPD patients compared with the non-COPD patients.

Our results suggested that pneumonia incidence rates were up to ten-fold higher in COPD patients starting from the period prior to initial diagnosis of COPD, and that the annual rate of increase was similar in the pre and post diagnosis periods when compared with similar patients without diagnosed COPD. Based on event rate ratios, cumulative incidence rates of pneumonia were higher among the COPD patients that preceded COPD diagnosis by two years. Over the 10-year period, ratios increased significantly on average by nearly 23% per year which was not different from that observed (22% per year) in the five-year period prior to COPD diagnosis. Trends in annual incidence rates of pneumonia were similar to that of the cumulative incidence rates. Pneumonia re-occurrences appeared to be uncommon in our cohorts. Total incidence rates were similar to annual incidence rates.

Three thousand seven hundred and fifty three ICS-exposed COPD patients were matched to an equal number of COPD patients never exposed to ICS. The two cohorts were sufficiently well balanced on the baseline characteristic variables. In the comparison between the ICS exposed and unexposed populations, we found no evidence of a pattern to suggest a strong association between ICS exposure and risk of pneumonia. Based on event rate ratios, we found no consistent evidence of differences in annual rates of incident pneumonia between the ICS exposed and unexposed groups. However, annual rates were significantly higher among those who became exposed in the last year prior to initiation of ICS and they remained marginally higher afterwards. Again, pneumonia re-occurrences appeared to be uncommon and total incidence rates levels were similar to annual incidence rates. However, rates were significantly higher in the exposed group in the year immediately prior to ICS initiation, thus supporting the association between COPD disease severity and risk of pneumonia.

Demographic Characteristics of Cohorts of COPD and Matched Non-COPD patients

		COPD N (%)	**Non-COPD N (%)**
Age at Matching			
	Age 45-64	3,460 (31.69%)	3,460 (31.69%)
	Age 65-74	3,970 (36.36%)	3,970 (36.36%)
	Age 75+	3,488 (31.95%)	3,488 (31.95%)
Gender			
	Female	5,241 (48.00%)	5,241 (48.00%)
	Male	5,677 (52.00%)	5,677 (52.00%)
Smoking Status			
	Non-Smoker	1,427 (13.07%)	4,388 (40.19%)
	Current	4,328 (39.64%)	1,437 (13.16%)
	Ex-smoker	2,485 (22.76%)	1,759 (16.11%)
	Unknown	2,678 (24.53%)	3,334 (30.54%)

*COPD patients and non-COPD patients were matched at time of diagnosis of COPD

Cumulative Incidence Rates of Pneumonia Among COPD and Matched Non-COPD*

	COPD patients			Non-COPD patients				
Year from COPD diagnosis	Cases (N)	Incidence per 1,000 person years	95% CI.	Cases (N)	Incidence per 1,000 person years	95% CI	Odds Ratio	95% CI
-5	30	1.96	(1.6,2.32)	4	0.57	(0.29,0.85)	3.44	(1.21,9.76)
-4	35	2.14	(1.78,2.5)	9	1.11	(0.74,1.48)	1.93	(0.93,4.02)
-3	45	2.66	(2.26,3.06)	14	1.52	(1.11,1.93)	1.75	(0.96,3.19)
-2	69	4.00	(3.52,4.48)	24	2.34	(1.86,2.82)	1.71	(1.07,2.72)
-1	172	15.96	(14.74,17.18)	17	1.57	(1.19,1.95)	10.17	(6.18,16.74)
0	128	12.29	(11.2,13.38)	16	1.48	(1.11,1.85)	8.30	(4.94,13.96)
1	140	15.16	(13.88,16.44)	26	2.69	(2.16,3.22)	5.64	(3.71,8.57)
2	129	18.06	(16.47,19.65)	28	3.74	(3.03,4.45)	4.83	(3.21,7.27)
3	93	16.92	(15.17,18.67)	12	2.07	(1.47,2.67)	8.17	(4.48,14.9)
4	75	17.78	(15.73,19.83)	14	3.13	(2.29,3.97)	5.68	(3.21,10.05)
*COPD patients and non-COPD patients were matched at time of diagnosis of COPD								
Annual Incidence Rates of Pneumonia Among COPD and Matched Non-COPD*								
	COPD patients			Non-COPD patients				
Year from COPD diagnosis	Cases (N)	Incidence per 1,000 person years	95% CI.	Cases (N)	Incidence per 1,000 person years	95% CI	Odds Ratio	95% CI
-5	30	3.95	(3.23,4.67)	4	0.53	(0.27,0.79)	7.45	(2.62,21.15)
-4	37	4.25	(3.55,4.95)	9	1.03	(0.69,1.37)	4.13	(1.99,8.56)
-3	47	4.81	(4.11,5.51)	14	1.43	(1.05,1.81)	3.36	(1.85,6.1)
-2	75	6.89	(6.09,7.69)	25	2.30	(1.84,2.76)	3.00	(1.91,4.72)
-1	191	17.49	(16.22,18.76)	18	1.65	(1.26,2.04)	10.60	(6.54,17.19)
0	140	12.82	(11.74,13.9)	16	1.47	(1.1,1.84)	8.72	(5.2,14.63)
1	160	14.65	(13.49,15.81)	26	2.38	(1.91,2.85)	6.16	(4.07,9.32)
2	141	16.53	(15.14,17.92)	29	3.40	(2.77,4.03)	4.86	(3.26,7.25)
3	111	16.55	(14.98,18.12)	13	1.94	(1.4,2.48)	8.53	(4.8,15.15)
4	95	18.60	(16.69,20.51)	16	3.13	(2.35,3.91)	5.94	(3.5,10.09)
*COPD patients and non-COPD patients were matched at time of diagnosis of COPD								
Cumulative Incidence Rates of Pneumonia Among COPD patients: ICS Exposed and Matched Unexposed*								

	ICS-exposed			ICS-unexposed				
Year from COPD diagnosis	**Cases (N)**	**Incidence per 1,000 person years**	**95% CI.**	**Cases (N)**	**Incidence per 1,000 person years**	**95% CI**	**Odds Ratio**	**95% CI**
-5	9	1.74	(1.16,2.32)	15	2.81	(2.08,3.54)	0.62	(0.27,1.42)
-4	8	1.44	(0.93,1.95)	19	3.35	(2.58,4.12)	0.43	(0.19,0.98)
-3	25	4.75	(3.8,5.7)	28	5.31	(4.31,6.31)	0.89	(0.52,1.53)
-2	27	5.67	(4.58,6.76)	41	8.68	(7.32,10.04)	0.65	(0.4,1.06)
-1	75	20.66	(18.27,23.05)	36	9.97	(8.31,11.63)	2.07	(1.39,3.08)
0	50	15.36	(13.19,17.53)	47	14.40	(12.3,16.5)	1.07	(0.72,1.59)
1	42	18.08	(15.29,20.87)	37	15.76	(13.17,18.35)	1.15	(0.74,1.79)
2	27	18.39	(14.85,21.93)	18	11.94	(9.13,14.75)	1.54	(0.85,2.8)
3	11	12.43	(8.68,16.18)	8	8.70	(5.62,11.78)	1.43	(0.58,3.56)
4	9	16.70	(11.13,22.27)	5	8.94	(4.94,12.94)	1.87	(0.63,5.58)
*COPD patients exposed to ICS and unexposed COPD patients were matched at time of initiation of ICS								
Annual Incidence Rates of Pneumonia Among COPD patients: ICS Exposed and Matched Unexposed*								
	ICS-exposed			ICS-unexposed				
Year from COPD diagnosis	**Cases (N)**	**Incidence per 1,000 person years**	**95% CI.**	**Cases (N)**	**Incidence per 1,000 person years**	**95% CI**	**Odds Ratio**	**95% CI**
-5	10	3.95	(2.7,5.2)	15	5.93	(4.4,7.46)	0.67	(0.3,1.49)
-4	8	2.63	(1.7,3.56)	19	6.25	(4.82,7.68)	0.42	(0.18,0.96)
-3	27	7.79	(6.29,9.29)	28	8.08	(6.55,9.61)	0.96	(0.57,1.63)
-2	29	7.73	(6.3,9.16)	44	11.72	(9.95,13.49)	0.66	(0.41,1.05)
-1	79	21.05	(18.68,23.42)	39	10.39	(8.73,12.05)	2.03	(1.38,2.98)
0	60	15.99	(13.93,18.05)	57	15.19	(13.18,17.2)	1.05	(0.73,1.51)
1	49	16.21	(13.89,18.53)	47	15.55	(13.28,17.82)	1.04	(0.7,1.55)
2	31	15.66	(12.85,18.47)	20	10.10	(7.84,12.36)	1.55	(0.88,2.72)
3	15	12.26	(9.09,15.43)	10	8.18	(5.59,10.77)	1.50	(0.67,3.34)
4	14	18.89	(13.84,23.94)	5	6.75	(3.73,9.77)	2.80	(1.01,7.77)
*COPD patients exposed to ICS and unexposed COPD patients were matched at time of initiation of ICS								
Conclusion: We found consistent evidence that pneumonia incidence was increased four- to tenfold in COPD patients compared to matched non-COPD patients, starting from the period prior to first diagnosis of COPD. In the comparison between the ICS exposed and unexposed COPD patients, we observed no evidence of an association between ICS exposure and increased risk of pneumonia in the first three years post-initiation of ICS, however pneumonia risk was significantly increased in the year prior to initiating ICS (OR=2.03) and four years after initiating ICS (OR=2.80) in a basic population-based cohort study design.								
Publications: No publication								

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