

Dabigatran is a relatively new selective, direct thrombin inhibitor shown to inhibit thrombin-induced cell proliferation, α -smooth muscle actin expression, and production of CTGF (14). Moreover, scleroderma lung myofibroblasts treated with dabigatran produce less CTGF, α -smooth muscle actin, and collagen type I (14). Dabigatran attenuated the development of bleomycin-induced pulmonary fibrosis in a murine model and significantly reduced thrombin activity and levels of TGF- β_1 and platelet-derived growth factor-AA in BALF (15). Histological lung inflammation and fibrosis were significantly decreased in dabigatran etexilate-treated mice (15).

The thrombin inhibition strategy for treatment of fibrosing lung diseases is very interesting and needs to be continued, but warfarin as a treatment of IPF should be contraindicated given the results of The AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) trial (2). We suggest that warfarin treatment for other indications (cardiac, thrombophlebitis, etc.) in case of IPF should also be prohibited and probably replaced by new anticoagulants such as dabigatran. On the other hand, a clinical trial to evaluate the efficacy of dabigatran in IPF is warranted. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Khuder Alagha, M.D.
Aix Marseille Université
Marseille, France

Veronique Secq, M.D.
INSERM U1068, Stress Cellulaire
Marseille, France

Laurie Pahun, M.D.
Tunde Sofalvi, M.D.
Alain Palot, M.D.
Aix Marseille Université
Marseille, France

Arnaud Bourdin, M.D., Ph.D.
Centre Hospitalier Universitaire Montpellier
Montpellier, France

Pascal Chanez, M.D., Ph.D.
Aix Marseille Université
Marseille, France

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Differential Effects of Inhaled Corticosteroids in Smokers/Ex-Smokers and Nonsmokers with Asthma

To the Editor:

Cigarette smoking decreases corticosteroid sensitivity in patients with asthma and worsens their symptoms and exacerbation frequency (1, 2). Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment. However, the optimal therapies for smokers with asthma are not well defined because smokers (and ex-smokers with a >10 pack-year history) are usually excluded from clinical trials (3, 4).

Supported by an unrestricted grant from Teva Pharmaceuticals Limited of Petach Tikva, Israel (for data acquisition and analysis). Access to data from the Optimum Patient Care Research Database was cofunded by Research in Real-Life Ltd.

Table 1. Summary of Key Baseline Patient Characteristics by Matched Treatment Cohorts and Smoking Status

Characteristic	Current/Ex-Smokers			Nonsmokers		
	Small-Particle ICS (n = 314)	Standard-Size-Particle ICS (n = 314)	P Value*	Small-Particle ICS (n = 575)	Standard-Size-Particle ICS (n = 575)	P Value*
Female sex, n (%)	187 (59.6)	187 (59.6)	N/A [†]	401 (69.7)	401 (69.7)	N/A [†]
Age at index date, yr, mean (SD)	49.2 (10.9)	49.1 (10.9)	0.40 [†]	49.7 (10.7)	49.6 (10.8)	0.57 [†]
30–60 yr of age, n (%)	250 (79.6)	250 (79.6)	N/A	457 (79.5)	457 (79.5)	N/A
61–70 yr of age, n (%)	64 (20.4)	64 (20.4)		118 (20.5)	118 (20.5)	
BMI in kg/m ² , mean (SD) [‡]	28.7 (6.9)	28.2 (6.0)	0.44	28.2 (6.1)	29.1 (6.7)	0.02
Time since first asthma prescription, n (%)						
Within 1 mo before index date	2 (0.6)	0 (0)	1.00	0 (0)	4 (0.7)	0.01
1–12 mo	38 (12.1)	38 (12.1)		55 (9.6)	66 (11.5)	
1–6 yr	110 (35.0)	116 (36.9)		187 (32.5)	213 (37.0)	
>6 yr	164 (52.2)	160 (51.0)		333 (57.9)	292 (50.8)	
Recorded comorbidity, n (%) [§]						
Rhinitis diagnosis	64 (20.4)	67 (21.3)	0.77	152 (26.4)	205 (35.7)	0.001
GERD diagnosis	42 (13.4)	41 (13.1)	0.91	69 (12.0)	82 (14.3)	0.26
Cardiac disease diagnosis	18 (5.7)	31 (9.9)	0.06	29 (5.0)	41 (7.1)	0.14
Risk-domain asthma control, n (%)	213 (67.8)	213 (67.8)	N/A [†]	393 (68.3)	393 (68.3)	N/A [†]
Spacer device used, n (%)	49 (15.6)	59 (18.8)	0.29	102 (17.7)	98 (17.0)	0.74
Recorded % predicted PEF, n (%)	212 (67.5)	251 (80.0)	<0.001	426 (74.1)	488 (84.9)	<0.001
% Predicted PEF, mean (SD)	82.9 (22.1)	81.9 (18.8)	0.92	85.0 (27.4)	85.1 (18.7)	0.75
Mean daily SABA dose, n (%)						
0 µg/d	11 (3.5)	11 (3.5)	0.59 [†]	53 (9.2)	53 (9.2)	0.31 [†]
1–100 µg/d	44 (14.0)	48 (15.3)		88 (15.3)	99 (17.2)	
101–200 µg/d	87 (27.7)	83 (26.4)		191 (33.2)	180 (31.3)	
201–400 µg/d	84 (26.8)	84 (26.8)		133 (23.1)	133 (23.1)	
>400 µg/d	88 (28.0)	88 (28.0)		110 (19.1)	110 (19.1)	
Mean daily ICS dose, n (%)						
1–50 µg/d	59 (18.8)	59 (18.8)	N/A [†]	97 (16.9)	97 (16.9)	N/A [†]
51–100 µg/d	85 (27.1)	85 (27.1)		159 (27.7)	159 (27.7)	
101–200 µg/d	90 (28.7)	90 (28.7)		190 (33.0)	190 (33.0)	
>200 µg/d	80 (25.5)	80 (25.5)		129 (22.4)	129 (22.4)	
LABA prescription (separate or FDC), n (%)	49 (15.6)	65 (20.7)	0.076	93 (16.2)	130 (22.6)	0.004
Severe exacerbations, n (%)						
0	239 (76.1)	239 (76.1)	N/A [†]	430 (74.8)	430 (74.8)	N/A [†]
1	47 (15.0)	47 (15.0)		100 (17.4)	100 (17.4)	
≥2	28 (8.9)	28 (8.9)		45 (7.8)	45 (7.8)	
Acute respiratory events, n (%)						
0	215 (68.5)	216 (68.8)	0.67	402 (69.9)	403 (70.1)	0.68
1	57 (18.2)	57 (18.2)		110 (19.1)	105 (18.3)	
≥2	42 (13.4)	41 (13.1)		63 (11.0)	67 (11.7)	
Asthma consultation/no oral corticosteroids, n (%)						
0	127 (40.4)	127 (40.4)	N/A [†]	206 (35.8)	206 (35.8)	N/A [†]
1	102 (32.5)	102 (32.5)		216 (37.6)	216 (37.6)	
≥2	85 (27.1)	85 (27.1)		153 (26.6)	153 (26.6)	
GP consultation for LRTI requiring antibiotic, n (%)						
0	254 (80.9)	271 (86.3)	0.11	508 (88.3)	505 (87.8)	0.50
≥1	60 (19.1)	43 (13.7)		67 (11.6)	70 (12.2)	

Definition of abbreviations: BMI = body mass index; FDC = fixed-dose combination; GERD = gastroesophageal reflux disease; GP = general practice; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LRTI = lower respiratory tract infection; N/A = not applicable; PEF = peak expiratory flow; SABA = short-acting β -agonist.

In each treatment cohort there were 119 (13.4%) current smokers and 195 (21.9%) ex-smokers (first recorded as ex-smokers at ≥ 30 yr of age).

*Matched cohorts were compared using conditional logistic regression.

[†]Matching variable (age matching was ± 5 yr).

[‡]Recorded BMI data were available for 861 (97%) and 853 (96%) patients in the small-particle ICS and standard-size-particle ICS cohorts, respectively.

[§]Diagnosis defined as database Read code for the condition.

^{||}The baseline doses of ICS were standardized to equivalence with small-particle beclomethasone and fluticasone; thus, doses of large-particle beclomethasone (Clenil Modulite) and budesonide were halved.

Exposure to even low levels of cigarette smoke is known to induce small airway inflammation (5, 6), which is associated with worse asthma control (5, 7). Therefore, ICS deposition in small airways, which increases with small- versus standard-size-particle ICS (8, 9), might be an important determinant of ICS effectiveness in smokers with asthma.

To explore this hypothesis, a historical matched cohort study was designed to compare the effectiveness of representative small-particle and standard-size-particle ICS for current and ex-smokers with asthma and to investigate any differential effect compared with effects in nonsmokers. Some of the results of this study have been previously reported in the form of abstracts (10, 11).

We examined anonymized medical record data for patients with asthma in two large UK electronic data sets, the General Practice Research Database (now in the Clinical Practice Research Datalink) and the Optimum Patient Care Research Database (12, 13). We studied patients aged 30–70 years when they were prescribed a step-up in asthma therapy of 50% or more increase in ICS dose, using hydrofluoroalkane beclomethasone dipropionate (Qvar; Teva Respiratory, LLC, Sellersville, PA; particles of median mass aerodynamic diameter, 1.1 μm) or fluticasone propionate (Flixotide; GlaxoSmithKline Australia Pty Ltd, Melbourne, Australia; median mass aerodynamic diameter, 2.4–3.2 μm) by pressurized metered-dose inhaler (14). Eligible patients had 2 consecutive years of data within the study period (January 1999–2010), including 1 baseline year before and 1 outcome year after the step-up index date, and remained at the stepped-up ICS dose during the outcome year, with at least one additional asthma prescription. Exclusion criteria were any chronic respiratory disease other than asthma, maintenance oral

corticosteroid therapy during baseline, multiple ICS prescriptions on the index date, and baseline or index date prescription of fixed-dose combination ICS plus long-acting β -agonist. Moreover, ex-smoking status had to be recorded at age 30 years or older to ensure long-term smoking. Patients stepped-up to small-particle ICS from 2005 onward were matched 1:1 to patients prescribed standard-size-particle ICS from 2000 onward to maximize patient numbers.

The primary effectiveness measure in this study was the rate of severe exacerbations, defined according to expert working group criteria (15) as an asthma-related emergency hospital attendance/admission or an oral corticosteroid pulse. Other effectiveness measures were the rate of acute respiratory events, defined as a severe exacerbation or general practice consultation for lower respiratory tract infection, and risk-domain asthma control, defined as the absence of any acute respiratory event.

Patients in small-particle and standard-size-particle ICS cohorts were matched sequentially in a 1:1 ratio for demographic characteristics and baseline markers of asthma severity, including sex, age (± 5 yr within subgroups of ≥ 30 –60 and > 60 –70 yr), smoking status, and baseline mean daily ICS dose, mean daily short-acting β -agonist dose, number of severe exacerbations, number of asthma consultations without oral corticosteroid prescription (i.e., without exacerbation), asthma control status, and index date year (± 5 yr).

Outcome year exacerbation and acute respiratory event rates were compared using conditional Poisson regression models. The adjusted odds of achieving risk-domain asthma control were compared using a conditional binary logistic regression model. Potential confounding variables considered were those that differed between cohorts at baseline ($P < 0.10$) and those that were

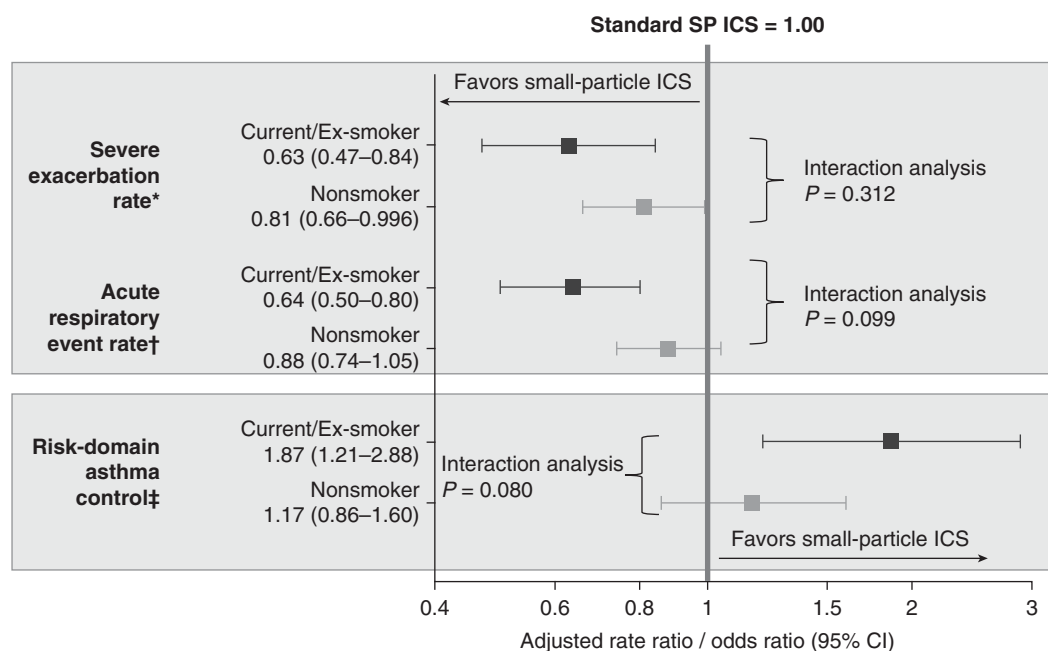


Figure 1. Adjusted outcome results for current/ex-smokers and nonsmokers prescribed small-particle ICS or standard-size-particle ICS, matched cohorts. *P* values are given for the interaction analysis. *Asterisk* indicates rate of severe exacerbations, adjusted for cardiac disease diagnosis, number of primary care consultations, and adherence to ICS therapy during baseline. *Dagger* indicates rate of acute respiratory events, adjusted for cardiac disease diagnosis, rhinitis diagnosis and/or therapy, number of primary care consultations, number of prescriptions for SABA, and LRTI consultations resulting in a prescription for antibiotics. *Double dagger* indicates odds of risk-domain asthma control, adjusted for rhinitis diagnosis and/or therapy, number of primary care consultations, adherence to ICS therapy, and LRTI consultations resulting in a prescription for antibiotics. CI = confidence interval; ICS = inhaled corticosteroid; LRTI = lower respiratory tract infection; SABA = short-acting β -agonist; standard SP = standard-size particle.

predictive ($P < 0.05$) of each outcome variable in multivariable analyses. All models included treatment, smoking status (current/ex-smoker vs. nonsmoker), and interaction between treatment and smoking status to determine any difference in treatment effect by smoking status. A P value less than 0.10 was considered significant for the exploratory interaction analysis. Analyses were performed using SPSS Statistics version 19 (SPSS Statistics, IBM, Somers, NY), SAS version 9.3 (SAS Institute, Cary, NC), and Microsoft Excel 2007 (Microsoft, Bellevue, WA).

After matching, there were 889 patients in each cohort, including 314 (35%) current or ex-smokers (Table 1). Nonsmokers in the standard-size-particle ICS cohort were more likely to have concomitant rhinitis or receive rhinitis therapy than nonsmokers in the small-particle ICS cohort. Patients in the standard-size-particle ICS cohorts were more likely to have been prescribed a long-acting β -agonist during the baseline year. Other differences between cohorts after matching were not clinically important.

On the index date, small-particle ICS was prescribed at significantly lower doses than standard-size-particle ICS (median [interquartile range (IQR)], 400 [200–400] vs. 500 [500–1,000] $\mu\text{g}/\text{d}$; $P < 0.001$). During the outcome year, ICS dose exposure was also significantly lower in the small-particle ICS cohort (median [IQR], 301 [164–438] $\mu\text{g}/\text{d}$ vs. 397 [238–658] $\mu\text{g}/\text{d}$; $P < 0.001$). The short-acting β -agonist dose was similar in the two cohorts (median [IQR], 219 [110–438] $\mu\text{g}/\text{d}$).

Adjusted rates of severe exacerbations during outcome were significantly lower for current/ex-smokers and nonsmokers in the small-particle than in the standard-size-particle ICS cohort, with no interaction between treatment and smoking status ($P = 0.31$; Figure 1). In contrast, for current and ex-smokers, adjusted rates of acute respiratory events were significantly lower, and adjusted odds of risk-domain asthma control significantly higher, with small-particle than with standard-size-particle ICS; for nonsmokers, no difference was found. The interaction between treatment and smoking status was significant at the 10% level for both of these outcomes (Figure 1).

When we examined results separately for smokers and ex-smokers, the same trends were observed for each group (as compared with nonsmokers): for risk-domain asthma control, the adjusted odds ratio (95% confidence interval) for small-particle ICS as compared with standard-size-particle ICS was 1.85 (0.96–3.58) for smokers, 1.88 (1.07–3.28) for ex-smokers, and 1.17 (0.86–1.60) for nonsmokers. Others have reported similarities in inflammation and treatment response between smokers and ex-smokers (16).

Another explanation for the similar findings for smokers and ex-smokers in this study could be the so-called “healthy smoker effect,” whereby patients with fewer respiratory symptoms tend to keep smoking and those with more symptoms tend to quit (17). Finally, an interaction between effects of age and smoking can be hypothesized because ex-smokers were older on average (mean [SD] age, 53 [10.2] yr) than smokers (43 [9.0]) and nonsmokers (50 [10.8]), and thus may have had more pack-years’ exposure than the current smokers.

These results confirm previous studies showing that in asthma, small-particle ICSs are at least as effective as standard-size-particle ICS despite being administered at significantly lower doses (18, 19). They also suggest a possible differential treatment effect with regard to smoking status and particle size of ICS, with a clear trend for greater beneficial effects of small-particle ICS for current/ex-smokers in terms of acute respiratory events and asthma control. This finding could be explained by increased small airway disease

induced by smoking and improved targeting of small airways by smaller ICS particles. Thus, small-particle ICS may be a preferred treatment choice for patients who are current or ex-smokers.

In any observational study, confounding (although limited by the matching process) and partial characterization of patients, most of whom lacked recorded lung function, must be considered. Another study limitation is the lack of detailed information on smoking history, which prevented us from examining the influence of smoke-free duration for ex-smokers and of pack-years for smokers and ex-smokers. As a result, the findings of this study should be considered exploratory. Nonetheless, we believe further investigation of a possible differential effect is warranted. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Nicolas Roche, M.D., Ph.D.
Cochin Hospital Group AP-HP
Paris, France
and
Paris Descartes University
Paris, France

Dirkje S. Postma, M.D., Ph.D.
University of Groningen
Groningen, The Netherlands

Gene Colice, M.D.
Washington Hospital Center
Washington, DC
and
George Washington University School of Medicine
Washington, DC

Anne Burden, M.Sc.
Research in Real Life, Ltd.
Cambridge, United Kingdom

Theresa W. Guilbert, M.D., M.S.
Cincinnati Children's Hospital and Medical Center
Cincinnati, Ohio

Elliot Israel, M.D.
Brigham and Women's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

Richard J. Martin, M.D.
National Jewish Health
Denver, Colorado

Willem M. C. van Aalderen, M.D.
Emma Children's Hospital AMC
Amsterdam, The Netherlands

Jonathan Grigg, M.D.
Queen Mary University of London
London, United Kingdom

Elizabeth V. Hillyer, D.V.M.
Julie von Ziegenweidt
Research in Real Life, Ltd.
Cambridge, United Kingdom

David B. Price, M.D.
Academic Primary Care
University of Aberdeen, United Kingdom
and
Research in Real Life, Ltd.
Cambridge, United Kingdom

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Empyema Necessitatis: Unique Presentation in a Coccidioidomycosis Case

Empyema necessitatis is a rare complication generally caused by tuberculosis (TB) (1). Pulmonary coccidioidomycosis causes empyema in less than 3% of cases (2–4) and has not previously been reported to cause empyema necessitatis. We present a patient with coccidioidomycosis with this unusual complication who was treated with percutaneous drainage and itraconazole.

Clinical Case

A 36-year-old Hispanic man from Monterrey, Mexico, presented with a 4-week history of a skin lesion on his right lower lateral chest wall. The lesion started as a macule that transformed into a 1-cm painless pustule that drained scarce pus and closed spontaneously, resulting in a scar. His past medical history was not significant. During the week before admission, he noticed a growing mass under the scar in the absence of fever and cough. Physical examination showed that the mass was a 5-cm, hot, fluctuant, painless subcutaneous collection, with a scar and redness close to its tip (Figure 1A). The complete metabolic panel and blood cell count were normal, and an HIV test was negative. A chest X-ray showed a thin-walled cavity in the right upper lobe and a right loculated pleural effusion that was confirmed by a computerized tomography scan that showed pleural effusion in communication with the subcutaneous fluid collection (Figure 1B). No pneumothorax was observed. A tap of the subcutaneous collection resulted in 300 ml odorless yellow pus. The pleural effusion almost disappeared after the tap, and the lung reexpanded. Gram and acid-fast bacillus stains were negative; however, a potassium hydroxide test showed abundant endospore-forming spherules characteristic of *Coccidioides immitis*. Fungi, bacterial, and acid-fast bacillus stains of bronchoalveolar lavage samples were negative. Skin test and complement fixation antibodies for *C. immitis* were negative. The patient refused surgery, and oral itraconazole 200 mg twice daily was initiated. In the third week of treatment, the subcutaneous collection and pleural effusion returned and were approximately a third of their original size, although the patient remained asymptomatic. A second tap of the subcutaneous collection drained 100 ml of pus. A potassium hydroxide test of the pus showed few spherules. *C. immitis* was found in both bronchoalveolar lavage samples and pus cultures. Itraconazole treatment was continued. By the second month, the subcutaneous collection had resolved and the pleural effusion had almost disappeared. The patient remained asymptomatic and was considered cured after the completion of a 12-month

Supported by the Hospital Universitario “Dr. Jose Eleuterio Gonzalez,” Universidad Autonoma de Nuevo León.

Author Contributions: Conception: A.R.; literature search and review: A.R., R.A.R., and O.B.; manuscript drafting and review: A.R., R.A.R., and O.B.

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