The Effect of Dipeptidyl-Peptidase-4 Inhibitors on Asthma Control: An Administrative Database Study to Evaluate a Potential Pathophysiological Relationship

Gene Colice,[1] David Price,[2] Maria Gerhardsson de Verdier,[1] Karma Rabon-Stith,[1] Chris Ambrose,[1] Kostubh Ranade,[1] Katherine Cappell,[3] Debra Irwin,[3] Paul Juneau,[3] Anna Vlahiotis[3]

[1]AstraZeneca, Gaithersburg, MD, USA; [2]University of Aberdeen, Aberdeen, UK; [3]Truven Health Analytics, an IBM Company, USA

Background

- Dipeptidyl-peptidase-4 (DPP-4) may play a role in the regulation of important immunological pathways implicated in asthma[1]
- Assessing a possible relationship between DPP-4 inhibitor (DPP-4i) use and asthma control is clinically important because of the increasing use of DPP-4i in type 2 diabetes mellitus management (T2DM)[2]

Objectives

- To identify possible associations between DPP-4i use and asthma control, relative to other anti-diabetes medications, using well-established administrative claims database research methods

Methods

- Study Design: Observational retrospective database study
- Data Sources: US administrative insurance claims data from the Truven Health (an IBM Company) MarketScan® Commercial and Medicare Supplemental Databases
  - These databases comprise enrolment and demographic information as well as inpatient medical, outpatient medical, and outpatient pharmacy claims data collected from employees, dependents, retirees, and members of more than 300 large self-insured US employers and more than 25 US health plans

Study Population

- Inclusion Criteria:
  - Adult asthma patients with comorbid T2DM newly initiating a DPP-4i or a non-DPP-4i antidiabetes medication between 11/1/2006 and 3/31/2014
    - Asthma identified as 1) at least one inpatient claim or one emergency department (ED) claim with a primary diagnosis for asthma (ICD-9-CM code 493.0x, 493.1x or 493.9x); 2) two or more other (i.e., non-ED) outpatient medical claims with an asthma diagnosis; or 3) at least one inpatient or outpatient medical claim with an asthma diagnosis along with at least one outpatient prescription claim for an asthma medication, including immunomodulators, inhaled corticosteroids (ICS), long-acting beta agonists (LABAs), ICS/LABA combinations, leukotriene modulators, mast cell stabilizers, short-acting beta agonists (SABAs), or xanthines
    - Date of the first of such pharmacy claims for a DPP-4i or non-DPP-4i was designated as the index date; the identity of the medication class on this claim determined the index medication class
  - At least 18 years old on the index date
  - At least one year of continuous enrolment in medical and pharmacy benefits prior to the index date (designated the baseline period), and at least one year of continuous enrolment in medical and pharmacy benefits after the index date (designated the follow-up period)
- Exclusion Criteria:
  - Any medical claims with an ICD-9-CM diagnosis code indicative of chronic obstructive pulmonary disease or chronic respiratory tract disease other than asthma during the baseline or follow-up periods
  - Any outpatient prescription drug claims for a DPP-4i during the baseline period
  - Non-DPP-4i patients were excluded if they had any outpatient prescription drug claims for any medication in the same non-DPP-4i medication class as their index prescription during the baseline period
- Two mutually exclusive study cohorts
  - **DPP-4i cohort:** newly initiated alogliptin, linagliptin, saxagliptin, sitagliptin, or combination products (e.g. pioglitazone/sitagliptin) on the index date
  - **Non-DPP-4i cohort:** newly initiated an alpha-glucosidase inhibitor, amylin analog, glucagon-like peptide-1 receptor agonist, meglitinide, sodium-glucose co-transporter 2 inhibitor, sulfonylurea, and/or thiazolidinedione on the index date
    - Metformin not included as a non-DPP-4i index medication because of the widespread prevalence of use of metformin as first-line T2DM therapy
    - Follow-up after the initial exposure (index date) was conducted in an intention-to-treat manner
- Outcomes:
  - **Risk-domain asthma control (RDAC):** Defined as no asthma hospitalizations, no lower respiratory tract infections (LRTI), and no oral corticosteroid (OCS) prescriptions[3]
  - **Overall asthma control:** RDAC criteria plus limited SABA use
  - **Treatment stability:** RDAC criteria plus no increase of ≥50% in ICS dose or addition of other asthma therapy between baseline and follow-up periods
  - **Number of severe asthma exacerbations:** Asthma-related hospitalizations or ED visits; or acute treatment with OCS (OCS prescription with ≤14 days' supply; or ≥14 days' supply + daily dosage greater than 10 mg)
- Matching: Patients in the DPP-4i cohort were directly matched to those in the non-DPP-4i cohort on several demographic and baseline covariates that were hypothesized to possibly affect the study outcomes
  - Age (within 5 years), sex, baseline number of acute OCS prescriptions, baseline SABA daily dose, baseline ICS daily dose, and baseline adapted Diabetes Complication Severity Index (aDCSI)4 score
  - DPP-4i patients were matched to non-DPP-4i patients at a 1:2 ratio, with 1:1 matched pairs substituted where 1:2 matching was not possible
- Statistical analyses:
  - Descriptive analyses compared demographic and clinical characteristics between DPP-4i and non-DPP-4i cohorts
  - RDAC, overall asthma control, and treatment stability during the follow-up period compared between the matched DPP-4i and non-DPP-4i cohorts using logistic regression
  - Number of severe asthma exacerbations during the follow-up period compared using a generalized linear regression model, assuming an underlying negative binomial distribution
  - Covariates in the logistic and negative binomial regression models included demographic characteristics not used for direct matching, diabetes- and asthma-related comorbidities, all diabetes- and asthma-related medication history measures not used for direct matching, and the Deyo-Charlson Comorbidity Index
  - For all outcomes, a p-value of < 0.05 was used to denote statistical significance

Results

Baseline Characteristics

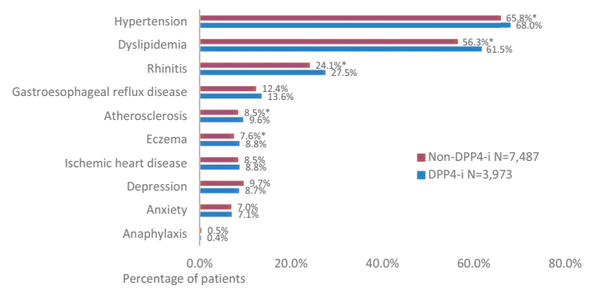
- A total of 3,973 patients selected in the DPP-4i cohort were matched to 7,487 patients in the non-DPP-4i cohort
  - 3,514 patients matched using 1:2 match ratio; 459 patients matched using 1:1 match ratio
- Although the DPP-4i cohort had both significantly higher mean Deyo-Charlson Comorbidity Index scores (2.22 vs. 2.11, p <0.05) and mean aDCSI scores (0.53 vs. 0.49, p <0.05) compared with the non-DPP-4i cohort, these differences were considered small and not clinically meaningful (Table 1)
- A significantly higher proportion of patients in the DPP-4i cohort had rhinitis, eczema, dyslipidemia, hypertension, and atherosclerosis than in the non-DPP-4i cohort (all p <0.05) (Figure 1)
- Asthma medication use during the baseline period was similar for the two cohorts
  - Overall, OCS utilization was low and mean SABA daily dose and mean ICS daily dose were also similar among the two cohorts

Table 1. Baseline Characteristics

CHARACTERISTIC	DPP-4-i N=3,973	Non-DPP-4-i N=7,487	p-value
Age (Mean, SD)[1]	53.7 (10.5)	53.4 (10.3)	0.150
Sex (N, %)[1]			0.563
Male	1,244 (31.3%)	2,305 (30.8%)	
Female	2,729 (68.7%)	5,182 (69.2%)	
General Health Status			
Deyo-Charlson Comorbidity Index (Mean, SD)	2.22 (1.2)	2.11 (1.1)	<0.0001
Adapted Diabetes Complication Score Index (Mean, SD)[1]	0.53 (1.0)	0.49 (0.9)	0.015

[1]used in direct matching

Figure 1. Baseline Comorbidities



*p ≤0.05

Asthma Control

- In the baseline period, there were no significant differences between the two cohorts in overall RDAC, overall asthma control, and number of severe asthma exacerbations
  - However, there were significant differences in two components of the RDAC relating to inpatient admissions, ED visits, and outpatient hospital visits for total LRTI and LRTI with an antibiotic prescription, but these differences were small
- During follow up, asthma control improved compared to baseline in both cohorts
- RDAC, overall asthma control, and number of severe asthma exacerbations were similar for the DPP-4i and non-DPP-4i cohorts also during follow-up (Table 2)
- Post-period treatment stability was also comparable between the DPP-4i and non-DPP-4i cohorts

Table 2. Asthma Control During Follow Up

CLINICAL CHARACTERISTIC	Baseline Period		Follow-up Period	
	DPP-4-i N=3,973	Non-DPP-4-i N=7,487	DPP-4-i N=3,973	Non-DPP-4-i N=7,487
Risk-Domain Asthma Control (N, %)				
Patients with no IP admission, ED, or OP hospital visit for asthma	3,133 (78.9%)	5,728 (76.5%)*	3,629 (91.3%)	6,717 (89.7%)*
Patients with no IP admission, ED or OP hospital visit for asthma visit for LRTI	3,816 (96.0%)	7,074 (94.5%)*	3,884 (97.8%)	7,266 (97.0%)*
Patients with no OP consultation for LRTI with a resultant antibiotic prescription	3,748 (94.3%)	7,119 (95.1%)	3,793 (95.5%)	7,173 (95.8%)
Patients with no prescriptions for an acute course of oral corticosteroid	2,507 (63.1%)	4,834 (64.6%)	2,917 (73.4%)	5,538 (74.0%)
Patients meeting all the above criteria indicating Risk-Domain Asthma Control	1,943 (48.9%)	3,655 (48.8%)	2,607 (65.6%)	4,894 (65.4%)
Overall Asthma Control (N, %)				
Patients with Risk-Domain Asthma Control AND limited SABA use (daily dose ≤180 mcg albuterol equivalents)	1,781 (44.8%)	3,353 (44.8%)	2,404 (60.5%)	4,533 (60.5%)
Number of Severe Asthma Exacerbations (N, %)				
0	2,264 (57.0%)	4,303 (57.5%)	2,823 (71.1%)	5,314 (71.0%)
1	1,162 (29.2%)	2,198 (29.4%)	757 (19.1%)	1,420 (19.0%)
2	320 (8.1%)	631 (8.4%)	235 (5.9%)	462 (6.2%)
≥3	227 (5.7%)	355 (4.7%)*	158 (4.0%)	291 (3.9%)
Number of Asthma Consultations Without Acute Oral Corticosteroids (N, %)[1]				
0	1,093 (27.5%)	2,174 (29.0%)	2,823 (71.1%)	5,314 (71.0%)
1	1,727 (43.5%)	3,345 (44.7%)	757 (19.1%)	1,420 (19.0%)
2	662 (16.7%)	1,182 (15.8%)	235 (5.9%)	462 (6.2%)
≥3	491 (12.4%)	786 (10.5%)	158 (4.0%)	291 (3.9%)
Treatment Stability				
Patients with Risk-Domain Asthma Control AND no asthma medication treatment change[2]	Not measured	Not measured	2,108 (49.0%)	6.098 (48.2%)

*p ≤0.05

[1]Used in direct matching;

[2]Treatment change was defined as either: (1) increased inhaled corticosteroid dose (≥50% change in average daily dose from the baseline period to the follow-up period) or (2) use of an asthma medication class during the follow-up period that was not used during the baseline period.

ED, emergency department; IP, inpatient; LRTI, lower respiratory tract infection; OP, outpatient; SABA, short-acting beta agonist

Multivariable analysis

- The adjusted odds of RDAC (OR: 1.05; 95% CI: 0.964 to 1.147), overall asthma control (OR: 1.04; 95% CI: 0.956 to 1.135), and treatment stability (OR: 1.04; 95% CI: 0.949 to 1.115) did not differ between the DPP-4i and non-DPP-4i cohorts (Figure 2A)
- After adjusting for baseline characteristics, no statistically significant difference was found between the DPP-4i and non-DPP-4i cohorts in the mean number of severe asthma exacerbations during the 12 months following initiation of anti-diabetes treatment (0.32 vs. 0.34 exacerbations per patient-year, respectively; p=0.064) (Figure 2B)

Figure 2a. Adjusted[1] Odds of Risk-Domain Asthma Control, Overall Asthma Control, and Treatment Stability during Follow Up

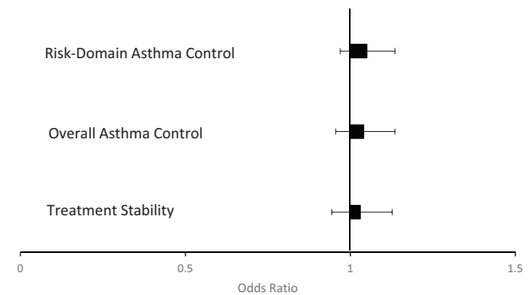
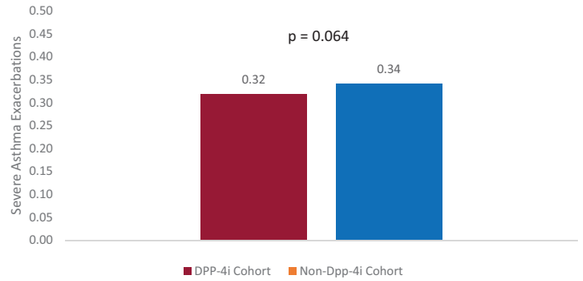


Figure 2b. Adjusted[1] Mean Estimated Number of Severe Asthma Exacerbations during Follow Up



[1]Models adjusted for health plan type, payer, geographic region, population density, index year, anaphylaxis, anxiety, depression, eczema, gastroesophageal reflux disease, ischemic heart disease, obesity, psoriasis, psoriasis, pulmonary hypertension, rhinitis, smoking, dyslipidemia, hypertension, renal impairment, baseline type 2 diabetes, number of asthma control medication prescriptions, number of asthma rescue medication prescriptions, number of antibiotic courses to treat LRTI, acetaminophen utilization, NSAID utilization, beta blocker utilization, microvascular complications of diabetes, macrovascular complications of diabetes, baseline biguanide utilization, baseline insulin utilization, baseline utilization of other antihyperglycemic medications, baseline DCI, baseline risk-domain asthma control, baseline overall asthma control, baseline number of severe asthma exacerbations and number of asthma consultations with acute OCS prescriptions

Conclusion

Asthma control was similar between patients initiating DPP-4i and non-DPP4i antidiabetes medications, suggesting little or no association between DPP-4i use and asthma control.

References

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Disclaimer

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