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DRUG SAFETY

Use of oral antidiabetic agents and risk of community-acquired pneumonia: a nested case–control study

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AIMS

To evaluate the association between use of different oral antidiabetic agents (OAD) and the risk of community-acquired pneumonia (CAP) in patients with type-2 diabetes (T2DM).

METHODS

Case–control study nested in a cohort of patients with T2DM and use of OAD between 2002 and 2013, based in a Spanish general practice research database. Cases were people diagnosed with T2DM, aged >18 years and with a validated diagnosis of CAP between 2002 and 2013. Ten controls were matched on age, sex and calendar year. Odds ratio (OR) of CAP was estimated comparing patients treated with: (1) metformin *vs.* other monotherapies or no antidiabetic treatment; (2) metformin + sulfonylureas *vs.* other antidiabetic combinations. OR of CAP was also assessed according to antidiabetic treatment duration.

RESULTS

From a cohort of 76 009 T2DM patients, we identified 1803 cases of CAP. No difference in the incidence of CAP was observed when comparing any OAD in monotherapy with metformin. Compared with current use of metformin + sulfonylurea, thiazolidinediones + metformin was associated with an increased risk of CAP (adjusted OR = 2.48, 95% CI 1.40–4.38). The use of any combination with thiazolidinediones was also associated with higher risk of CAP (adjusted OR = 2.00, 95% CI 1.22–3.28). Current use of DPP-4 inhibitors was not associated with an increased risk of CAP.

CONCLUSIONS

No differences in the incidence of CAP were observed between the use of OAD in monotherapy *vs.* metformin. Thiazolidinedione use in combination was associated with an increase in the risk of CAP when compared to metformin + sulfonylureas. The use of DPP-4 inhibitors was not associated with an increased risk of CAP.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Some antidiabetics have been associated with immune system disorders, leading to an increase in the incidence of infections.
- Lower respiratory tract infections, such as community-acquired pneumonia, are common in patients with diabetes.
- Case–control studies based in well-validated epidemiological databases are very useful in exploring these potential side effects.

WHAT THIS STUDY ADDS

- The use of thiazolidinediones in combination doubled the risk of CAP when compared to metformin + sulfonylurea.
- No antidiabetic monotherapy compared to metformin showed an increased risk of CAP.
- The estimated incidence of CAP in type 2 diabetic patients was 6.04/1000 person-years, higher than in the general population.

Tables of Links

TARGETS	
GPCRs [2]	**Enzymes** [4]
GLP-1 receptor	α-glucosidase
Nuclear hormone receptors [3]	DPP-4
PPARδ	
PPARγ	

LIGANDS	
Exenatide (exendin-4)	Liraglutide
GLP-1	Sitagliptin
Insulin	Vildagliptin

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2–4].

Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases, with an incidence of 5–11 per 1000 adults per year and a hospital admission incidence of 1–4 per 1000 adults per year [5]. In Spain an incidence of 2.69 cases per 1000 person-years was observed in a study using the BIFAP database (Database for Pharmacoepidemiology Research in Primary Care) [6]. Along with influenza, CAP was the eighth leading cause of death in Spain in 2012 [7]. Moreover, patients with diabetes have an increased incidence of pneumonia, complications associated therewith, and mortality [5, 8].

Oral antidiabetics act on different biological targets and some of these have been associated with immune system disorders, including an increase in the incidence of infections. Thiazolidinedione use was associated with a higher incidence of pneumonia in a meta-analysis of clinical trials, [RR = 1.40 (95% CI 1.08 to 1.82) $P < 0.05$; $I^2 = 0\%$] [9].[1] Also, an increase in the number of infections, mainly upper respiratory tract infections, has recently been associated with the use of dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) [10]. A Cochrane review found a higher incidence of infections associated with sitagliptin in short-term clinical trials (<6 months). In the case of vildagliptin, a trend towards increased incidence of infections was observed, though statistical significance was not reached [11].

Large epidemiological databases can be useful tools to evaluate the association of specific treatments with the incidence of CAP, as shown in two case–control studies reporting an increase in the incidence of CAP associated with proton-pump inhibitors [12, 13]. Therefore, the aim of this study was to evaluate the association between the current use of different oral antidiabetic agents and the risk of CAP in a cohort of patients with type 2 diabetes identified from a large database including primary care health records in Spain.

[1]Thiazolidinedione use in combination might increase the risk of pneumonia when compared to metformin + sulfonylureas.

Methods

Study design and setting

A case–control study nested in a cohort was carried out using the information from BIFAP (*Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria*, Database for Pharmacoepidemiological Research in Primary Care). This is a longitudinal population-based database managed by the Spanish Agency for Medicines and Medical Devices that collates, from 2000 onwards, the computerized

medical records of more than 5800 primary care physicians throughout Spain. It includes anonymized information on over 8 million patients, totalling over 46.2 million person-years of follow-up. BIFAP contains information about demographic data, medical diagnoses, clinical data and drug prescriptions [14]. Since 2002 a number of studies have been performed in order to validate the information included in BIFAP [15, 16] and the CAP incidence in this database has been reported previously [6].

This project was approved by the Navarre Research Ethics Board, Pamplona, Spain. All data were anonymized and no written informed consent was necessary for this type of study according to the Spanish regulations [17].

Participants

Study cohort

All patients older than 18 years with a diagnosis of type 2 diabetes mellitus (T2DM) or non-specified diabetes were selected according to the International Classification in Primary Care (ICPC) codes. Patients should have also initiated treatment with an oral antidiabetic drug (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides or dipeptidyl peptidase-4 inhibitors or their combinations) between 1 January 2002 and 31 December 2013 and have at least 1 year of follow-up in BIFAP before the entry date was required. Concomitant treatment with insulin was not an exclusion criterion.

Cohort entry was defined by the date of first oral antidiabetic drug prescription for patients aged 19 or older and who had been followed for at least 1 year in BIFAP. Patients with an oral antidiabetic drug prescription before 1 January 2002 or before the age of 18 were excluded. Patients with any history of cancer before start date (except non-melanoma skin cancer) were also excluded because they might have received treatments not recorded in the BIFAP database.

Patients were followed until the occurrence of one of the following end-points: pneumonia (potential case), cancer, death, loss to follow-up or end of study period (31 December 2013), whichever came first.

Selection of cases and controls

A nested case–control analysis was conducted in this cohort study. A nested case–control study refers to a case–control study conducted in a fully enumerated cohort, allowing the identification of all cases occurring in the cohort and the random sampling of controls, without risking selection bias. This is a more efficient approach than analysing the entire cohort [18]. Cases were defined as any subject of the cohort with a diagnosis of CAP. The International Classification of Primary Care (ICPC) is a classification of the most frequent health problems in primary care with limited granularity (~700 codes). The most common descriptors of each ICPC are indexed in BIFAP by adding a fourth digit to the ICPC code of reference (1,2,...,n), hereafter called ICPC-BIFAP codes. The computer search for cases looked for the ICPC-BIFAP codes for pneumonia (R81.01, R81.02, R81.03, R81.04, R81.05, R81.06, R81.07, R81.08, R81.09, R81.10, R81.11 and R81.13), semantic chains compatible with pneumonia in the Table of Diagnoses (doctors can modify the text corresponding to an ICPC code) or the word 'pneumonia' in free text clinical notes. If the text in the diagnosis section was 'nosocomial pneumonia' (R81.12) or 'aspiration pneumonia' (R99.6), the record was assigned to the end-point 'non-community acquired pneumonia'. The corresponding truncated Spanish terms were used.

For each case, up to 10 controls without CAP by the time of the index date were matched on age (±1 year), sex and calendar year by risk set sampling. The date of CAP diagnosis served as the index date for cases and their matched controls.

Case validation

BIFAP is a computerized database gathering information provided by general practitioners and paediatricians working in the Spanish National Health Service. It includes diagnosis and medical tests among other information. Patients attended the hospital Emergency Service department and underwent chest radiography, the results of which are reported to the general practitioner, though the radiographic images are kept in the hospital. Patients diagnosed with CAP at the hospital level were included in our study. In order to avoid false positive diagnosis of CAP, we excluded patients diagnosed with CAP at primary care setting with no evidence of chest radiography in the clinical record, regardless of whether sign and symptoms were compatible with a diagnosis of CAP.

All potential cases were reviewed and validated by two different investigators using an extract from the database covering ±90 days around the pneumonia diagnosis date. Discrepancies were resolved by consensus between the two reviewers. During validation, investigators were blinded to the drug treatment.

Potential cases were considered valid if they fulfilled the following criteria: (1) CAP occurred after the first prescription of an oral antidiabetic drug (incident cases); (2) there was no cancer diagnosis prior to the pneumonia date and a non-community acquired origin was excluded; and (3) diagnosis was confirmed by means of any of the following criteria: it was made by a specialist or in a hospital or emergency department setting, there was a radiology record that confirmed diagnosis, there was a laboratory record that confirmed diagnosis (e.g. positive urinary antigen to *Legionella pneumophila*), or the specific anatomic site of pneumonia was registered.

Study size

Assuming a diabetes prevalence of 6% and an annual incidence of pneumonia of 1% during the 4 years of the study, it was expected that about 7200 cases would be obtained. According to prescription data of the Navarre Health Service in 2010 (unpublished internal data of the Navarre Health Service, Pamplona, Spain), 50% of patients used metformin, 20% sulfonylureas, 11% DPP-4 inhibitors, 9% meglitinides, 3% alpha-glucosidase inhibitors and 2% thiazolidinediones. It was estimated that, in the group with the lowest consumption of antidiabetics, at least 580 cases could be identified. This provides a statistical power greater than 90% to detect an increase/decrease in risk of 75% (OR = 1.75), assuming an alpha error of 5% and a prevalence of exposure of 5%.

Medication use and other covariates

Use of oral antidiabetic drugs [ATC codes: metformin (A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11), sulfonylureas (A10BB, A10BD02, A10BD04, A10BD06), alpha-glucosidase inhibitors (A10BF), thiazolidinediones (A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09), dipeptidyl peptidase-4 inhibitors (A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11), meglitinides (A10BX02 y A10BX03)] before the index date was obtained from the computerized database.

Individuals were classified as *current vs. not current* users for the oral antidiabetic treatment. Current use was considered when the last prescription ended <30 days from index date, which is the standard number of days of supply for most prescriptions in the primary care system in Spain.

Two different reference groups were used for the primary analysis: (1) When current users were treated with just one or no oral antidiabetic drug, then metformin was chosen as the reference; (2) When current users were treated with two or more oral antidiabetic drugs, then metformin plus a sulphonylurea was selected. Current users of oral antidiabetic drugs were also subdivided *a priori* into three categories taking into account the duration of these treatments: 1–30 days (reference group), 31–180 days and >180 days.

Information on comorbidities and use of other medications was obtained as potential confounders to adjust for in all statistical models. As relevant comorbidities, the following conditions were chosen (ICPC or ICPC-BIFAP codes): prior pneumonia (R81), chronic obstructive pulmonary disease (COPD) (R95), asthma (R96), alcohol abuse (P15), heart failure (K77), kidney disease (U59.01, U99), cirrhosis (D97), coronary artery disease (K74, K75, K76), stroke (K90, K91), dementia (P70), Parkinson's disease (N87), dysphagia (D21), AIDS (B90.01, B90.02), diabetic retinopathy (F83), nephropathy (T90.11, U88), diabetic neuropathy (T89.03, T90.12, N94) and any diabetes complication (T89.03, T90.11, T90.12, U88, N94, F83). Patients were considered exposed when there was a registered ICPC code before the index date.

Concomitant medications registered (ATC codes) were as follows: antibiotics (J01), antituberculosis drugs (J04A), anti-dementia drugs (N06D), antipsychotics (N05A), anti-Parkinson's disease drugs (N04A), inhaled corticosteroids (R03BA, R03AK06, R03AK07), systemic corticoids (H02A, H02B), immunosuppressive therapy (L04AA, L04AB, L04AC L04AD, L04AX), proton pump inhibitors (A02BC, M01AE52), insulins (A10A), GLP-1 agonists (A10BX04, A10BX07), opioids (N02A) and drugs for asthma or COPD (R03). Patients were considered exposed when the last prescription occurred <90 days from index date.

Other variables such as body mass index (BMI, last measure <2 years from index date, in kg m^{-2}), smoking status (last measure before index date, classified as 'Yes/No/Past smoker') and time since diabetes diagnosis (years) were obtained from the database as well.

Statistical analyses

Descriptive statistics were used to summarize the baseline characteristics of cases and controls. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of CAP associated with current use of (1) metformin *vs.* other oral antidiabetic agents in monotherapy or (2) metformin and sulfonylureas *vs.* other combinations of at least two oral antidiabetic agents.

The model was adjusted for age, BMI, smoking status, time since diabetes diagnosis, medications and comorbidities. Regarding medications, the model was adjusted for the time since first oral antidiabetic prescription, current antibiotic use (<90 days from index date), anti-dementia drugs, medications for Parkinson's disease, antipsychotics, asthma and COPD medications, inhaled or systemic corticosteroids, proton pumps inhibitors, insulin or opioids use at the index date. As comorbidities, the model was adjusted for alcohol abuse, asthma, dementia, dysphagia, stroke, coronary artery disease, COPD, heart failure, kidney disease, prior pneumonia (before cohort entry) and Parkinson's disease.

Due to their very low prevalence, the following covariates were not included in the model: tuberculostatic drugs, GLP-1 agonists, immunosupressive medications, cirrhosis, any diabetes complication, nephropathy, diabetic neurophaty, diabetic retinopathy and HIV/AIDS.

The effects of duration of oral antidiabetic treatment on the incidence of CAP were also evaluated as a secondary outcome. Duration of treatment was categorized as ≤30 days, 31–180 days or >180 days.

As a sensitivity analysis, the primary analysis was repeated defining current use of antidiabetic medication if the last prescription ended <90 days before index date (instead of <30 days for the main analysis). Also, the influence of concomitant antidiabetic drugs was post-hoc evaluated according to Faillie and colleagues [19]. Exposure to antidiabetic drugs was assessed at the index date and defined hierarchically according to the following six mutually exclusive categories: (i) current use of DPP-4 inhibitors or thiazolidinediones; (ii) current use of GLP-1 analogues such as exenatide or liraglutide; (iii) current use of insulin; (iv) current use of metformin and sulfonylurea; (v) current use of other oral antidiabetic agent; and (vi) no current use of an antidiabetic agent at index date. Another primary analysis was done excluding users of insulin.

Results

Participants

From a cohort of 76 009 patients diagnosed with type 2 diabetes, 2966 potentially eligible cases between 2002 and 2013 were identified. Of these, 1803 cases of CAP were validated. Of the remainder, 589 records were classified as non-cases and 574 lacked enough information to make a decision.

A total of 17 986 controls were matched to the confirmed 1803 cases from the cohort. Of these 1803 cases, 1774 were matched with 10 controls and for 29 cases the matching criteria were softened using larger intervals for age (± 5 years).

The mean age of cases (± SD) was 71.7 ± 12.4 years. Overall, cases had a higher prevalence of co-morbidities and drug use than controls, while the time since diabetes diagnosis and oral antidiabetic use was similar between cases and controls (Table 1).

Table 1

Baseline characteristics of cases and controls at index date

	Case (*n* = 1803)				Control (*n* = 17 986)			
	n	%	Mean	SD	*n*	%	Mean	SD
Age			71.7	12.4			71.6	12.3
Women	665	36.9			6639	36.9		
BMI			30.5	6.0			30.2	5.3
<18.5	8	0.4			31	0.2		
18.5–24.9	175	9.7			1570	8.7		
25.0–29.9	499	27.7			5548	30.9		
30.0–34.9	398	22.1			4273	23.8		
35.0+	248	13.8			2004	11.1		
Not available	475	26.3			4560	25.4		
Current smoking	44	2.4			328	1.8		
Time since diabetes diagnosis, yrs			5.6	4.4			5.2	4.2
Current oral antidiabetic use (<30 days from index date)								
Metformin	971	53.9			9722	54.1		
Sulfonylureas	415	23.0			3890	21.6		
Alpha-glucosidase inhibitors	36	2.0			449	2.5		
Thiazolidinediones	34	1.9			238	1.3		
Dipeptidyl peptidase-4 inhibitors	128	7.1			1038	5.8		
Meglitinides	129	7.2			1020	5.7		
None	450	24.9			4668	25.9		
No antidiabetic treatment[a]	407	22.6			4348	24.2		
No. of current oral antidiabetics			1.0	0.7			0.9	0.7
Current medication use (<90 days from index date)								
Antibiotic	497	27.6			2507	13.9		
Anti-dementia	38	2.1			380	2.1		
Anti-Parkinson's disease	44	2.4			261	1.5		
Antipsychotics	95	5.3			712	4.0		
Asthma/COPD	543	30.1			1882	10.5		
Inhaled corticosteroids	411	22.8			1289	7.2		
Systemic corticosteroids	176	9.8			537	3.0		
Proton pump inhibitors	865	48.0			6967	38.7		
Insulin	125	6.9			793	4.4		
Opioids	152	8.4			1077	6.0		
Comorbidities								
Alcohol abuse	75	4.2			474	2.6		
Asthma	160	8.9			912	5.1		
Dementia	55	3.1			505	2.8		
Dysphagia	17	0.9			136	0.8		
Stroke	103	5.7			946	5.3		
Coronary artery disease	263	14.6			1910	10.6		

(*continues*)

Table 1

(Continued)

	Case (*n* = 1803)				Control (*n* = 17 986)			
	n	%	Mean	SD	*n*	%	Mean	SD
COPD	332	18.4			1263	7.0		
Heart failure	212	11.8			800	4.5		
Kidney disease	126	7.0			837	4.7		
Prior pneumonia	181	10.0			527	2.9		
Parkinson's disease	26	1.4			169	0.9		

BMI = body mass index; SD = standard deviation; yrs = years; COPD = chronic obstructive pulmonary disease
[a]No current use of oral antidiabetic nor insulin

Outcome data

The results of the primary analysis are shown in Table 2. When comparing any antidiabetic agent in monotherapy with metformin, no difference in the incidence of CAP was observed after adjustment. Compared with current use of metformin plus sulfonylurea, the use of thiazolidinediones plus metformin was associated with an increased risk of CAP (adjusted OR 2.48, 95% CI 1.40–4.38). No other statistically significant differences between the other combinations were observed.

Sensitivity analyses

The results remained similar after using a broader definition of *current use* (<90 days since the end of last prescription) (Table 3).

According to the post-hoc analysis, the use of any combination including thiazolidinediones was associated with a higher risk of CAP [OR 2.00 95% CI (1.22–3.28)] (Table 4) and also with any combination of meglitinides and other oral antidiabetic drugs [OR 1.47 95% CI (1.01–2.12)] (Table 5) *vs*. metformin plus sulfonylureas. No statistically significant differences were found when comparing the use of DPP-4 inhibitors (Table 6).

No correlation between treatment duration and risk of CAP was observed when comparing the use of DPP-4 inhibitors, meglitinides or thiazolidinediones combined with other antidiabetic drugs *vs*. metformin plus sulfonylureas (Tables 7, 8 and 9).

Table 2

Association of current use (defined as <30 days since end of last prescription) of oral antidiabetic drugs exposure with community acquired pneumonia

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin, alone	678	37.6	7262	40.4	1	Reference	1	Reference
No treatment	447	24.8	4638	25.8	1.02	0.90–1.16	0.97	0.84–1.11
Sulfonylureas, alone	244	13.5	2355	13.1	1.09	0.93–1.28	0.99	0.84–1.18
Alpha-glucosidase inhibitors, alone	18	1.0	259	1.4	0.73	0.45–1.19	0.72	0.43–1.19
Thiazolidinediones, alone	4	0.2	48	0.3	0.89	0.32–2.48	0.75	0.26–2.17
Dipeptidyl peptidase-4 inhibitors, alone	17	0.9	136	0.8	1.35	0.80–2.25	1.32	0.77–2.28
Meglitinides, alone	75	4.2	596	3.3	1.35	1.04–1.74	1.02	0.78–1.35
Metformin + sulfonylureas	121	6.7	1147	6.4	1	Reference	1	Reference
Metformin + alpha-glucosidase inh	2	0.1	50	0.3	0.38	0.09–1.59	0.44	0.11–1.84
Metformin + thiazolidinediones	18	1.0	71	0.4	2.41	1.39–4.18	2.48	1.40–4.38
Metformin + DPP4 inhibitors	80	4.4	644	3.6	1.20	0.88–1.62	1.20	0.88–1.66
Metformin + Meglitinides	39	2.2	254	1.4	1.47	1.00–2.16	1.44	0.97–2.16
Other combinations of two drugs	25	1.4	222	1.2	1.09	0.69–1.72	1.14	0.72–1.83
Other combinations of three or more drugs	35	1.9	304	1.7	1.09	0.73–1.62	1.00	0.66–1.51

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Table 3

Association of current use (defined as <90 days since end of last prescription) of oral antidiabetic drugs exposure with community acquired pneumonia

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin, alone	733	40.7	8004	44.5	1	Reference	1	Reference
No treatment	272	15.1	3028	16.8	0.97	0.84–1.13	0.91	0.78–1.07
Sulfonylureas, alone	285	15.8	2666	14.8	1.16	0.99–1.35	1.07	0.91–1.26
Alpha-glucosidase inhibitors, alone	22	1.2	282	1.6	0.85	0.54–1.32	0.84	0.53–1.32
Thiazolidinediones, alone	4	0.2	49	0.3	0.89	0.32–2.47	0.73	0.24–2.20
Dipeptidyl peptidase-4 inhibitors, alone	16	0.9	136	0.8	1.28	0.75–2.17	1.35	0.78–2.35
Meglitinides, alone	83	4.6	637	3.5	1.42	1.11–1.81	1.09	0.84–1.42
Metformin + sulfonylureas	161	8.9	1409	7.8	1	Reference	1	Reference
Metformin + alpha-glucosidase inh	1	0.1	60	0.3	0.15	0.02–1.06	0.16	0.02–1.17
Metformin + thiazolidinediones	21	1.2	84	0.5	2.18	1.31–3.61	2.25	1.33–3.80
Metformin + DPP4 inhibitors	84	4.7	681	3.8	1.09	0.82–1.45	1.10	0.81–1.48
Metformin + Meglitinides	45	2.5	308	1.7	1.29	0.91–1.84	1.26	0.87–1.81
Other combinations of two drugs	27	1.5	247	1.4	0.98	0.63–1.50	0.96	0.62–1.50
Other combinations of three or more drugs	49	2.7	395	2.2	1.08	0.77–1.52	0.99	0.69–1.41

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Table 4

Association of thiazolidinediones (TZD) in combination *vs* metformin + sulfonylureas (SU) with risk of pneumonia, BIFAP. Mutually exclusive categories. TZD combination as separate category

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin + SU	121	6.7	1147	6.4	1	Reference	1	Reference
Thiazolidinediones + other drug	24	1.3	113	0.6	2.02	1.25–3.27	2.00	1.22–3.28

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Table 5

Association of meglitinide in combination *vs* metformin + sulfonylureas (SU) with risk of pneumonia, BIFAP. Mutually exclusive categories. Meglitinide combination as separate category

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin + SU	121	6.7	1147	6.4	1	Reference	1	Reference
Meglitinide + other drug	48	2.7	325	1.8	1.42	0.99–2.03	1.47	1.01–2.12

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Table 6

Association of Dipeptidyl peptidase-4 (DPP4) inhibitors *vs* metformin + sulfonylureas (SU) with risk of pneumonia, BIFAP. Mutually exclusive categories. DPP-4 inhibitors as separate category

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin + SU	117	6.5	1114	6.2	1	Reference	1	Reference
DPP-4 inhibitors	128	7.1	1038	5.8	1.21	0.92–1.59	1.19	0.90–1.58

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Table 7

Association of Dipeptidyl peptidase-4 (DPP4) inhibitors *vs* metformin + sulfonylureas (SU) with risk of pneumonia according to treatment duration, BIFAP. Mutually exclusive categories. DPP-4 inhibitors as separate category

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin and SU	117	6.5	1114	6.2	1	Reference	1	Reference
Duration of DPP-4 inhibitors								
1–30 days	14	0.8	101	0.6	1.35	0.74–2.44	1.37	0.74–2.54
31–180 days	35	1.9	289	1.6	1.18	0.79–1.77	1.20	0.79–1.82
>180 days	79	4.4	648	3.6	1.20	0.88–1.64	1.16	0.84–1.60
p for trend					0.79		0.60	

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Table 8

Association of meglitinide in combination *vs* metformin + sulfonylureas (SU) with risk of pneumonia according to treatment duration, BIFAP. Mutually exclusive categories. Meglitinide in combination as separate category

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95%CI	OR	95%CI
Metformin + SU	121	6.7	1147	6.4	1	Reference	1	Reference
Duration of meglitinide + other drug								
1–30 days	2	0.1	41	0.2	0.47	0.11–1.98	0.62	0.15–2.56
31–180 days	15	0.8	76	0.4	1.89	1.05–3.39	2.00	1.08–3.69
>180 days	31	1.7	208	1.2	1.43	0.94–2.19	1.44	0.93–2.23
p for trend					0.48		0.78	

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

Discussion

Key results

In our study, the incidence of CAP was 6.04 cases per 1000 person-years which is within the range observed in other studies [20]. The use of thiazolidinediones plus metformin *vs*. metformin plus sulfonylureas was associated with an increase in the risk of CAP. A higher risk of CAP was also found between the use of any combination of oral antidiabetic drugs plus thiazolidinediones *vs*. metformin plus sulfonylureas. This result is consistent in our different sensitivity analyses. This higher risk was also found in a meta-analysis [21] of randomized clinical trials in patients with pneumonia and lower respiratory tract infection (RR 1.40, 95% CI 1.08–1.82). No statistically significant differences in the incidence of CAP were observed between the use of thiazolinediones alone *vs*. metformin. However,

Table 9

Association of thiazolidinediones (TZD) in combination *vs* metformin + sulfonylureas (SU) with risk of pneumonia according to treatment duration, BIFAP. Mutually exclusive categories. TZD in combination as separate category

	Cases		Controls		Model adjusted for age		Model adjusted for several factors[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Metformin and SU	121	6.7	1147	6.4	1	Ref	1	Ref
Duration of TZD + other drug								
1–30 days	2	0.1	10	0.1	1.87	0.41–8.61	1.49	0.28–7.86
31–180 days	7	0.4	26	0.1	2.57	1.08–6.12	2.94	1.22–7.08
>180 days	15	0.8	77	0.4	1.86	1.04–3.34	1.72	0.94–3.15
p for trend					0.33		0.32	

[a]Conditional logistic regression adjusted for age, BMI, smoking, time since diabetes diagnosis, all medications and comorbidities listed in Table 1, and time since first oral antidiabetic prescription

this could be due to the small size in the thiazolidinedione group (four cases only).

Several mechanisms by which thiazolidinediones could increase the risk of pneumonia have been proposed [21] but uncertainty remains. Thiazolidinedione are peroxisome proliferator-activated receptor gamma (PPARγ) agonists. Activation of PPARγ has anti-inflammatory effects and reduces the function of immune cells [22]. These glucocorticoid-like effects in the respiratory tract could lead to an increased susceptibility to infection. In addition, thiazolidinediones are claimed to have proinflammatory actions in human macrophages through an off-target effect on PPARδ [23]. Based on that, additional studies are needed to clarify all these effects potentially linked to pneumonia and other infections.

The use of other treatments was not associated with an increased risk of CAP compared with the use of metformin + sulfonylureas. An association between DPP-4 inhibitors use and CAP was not found. This result is in line with a meta-analysis of randomized clinical trials that showed sitagliptin did not increase the risk of pneumonia [24]. Two observational studies carried out in the UK Clinical Practice Research Datalink (CPRD) found no association between the use of DPP-4 inhibitors and the risk of hospitalization from CAP [19] or pneumonia [25].

Similarly, no association between the risk of CAP and the use of sulfonylureas, alpha-glucosidase inhibitors or meglitinides in monotherapy was found compared to metformin. No association was observed in the main analysis between the use of metformin combined with either alpha-glucosidase inhibitors or meglitinides compared to metformin + sulfonylureas. However, a post-hoc analysis including all types of combinations with meglitinides did not support this finding, showing a higher risk of CAP linked to these drugs.

A high proportion of patients did not have recorded antidiabetic treatment at the index date (24.9% of the cases). As a result, it was decided to undertake a sensitivity analysis considering current use as <90 days since the last prescription. The results were similar in all groups.

Some drugs, such as DPP-4 inhibitors or thiazolidinediones [5], are used as a second or third line of treatment. In order to reduce potential confounding by indication, several comparisons were carried out. First, the effects of antidiabetic drugs in monotherapy was tested *vs.* metformin. Second, the main antidiabetic drugs in combination with metformin were compared to metformin + sulfonylureas (the most common combination treatment). And third, antidiabetic drugs in combination with any other oral hypoglicaemic drug were compared to metformin + sulfonylureas. The results were robust and indicated an increase in the risk of CAP associated with the use of thiazolidinediones and with no different risk with DPP-4.

As stated previously, results with meglitinides were particularly uncertain. There was a borderline increase in the risk of CAP in some comparisons but not in others. Moreover, results also changed when the definition of current use (as <90 days) was modified. Further studies are needed to clarify the association of meglitinides use with risk of CAP.

One of the inclusion criteria was 'current use of oral antidiabetic agents'. The first prescription date was used as the date for inclusion in the cohort. Previous use of insulin was not an exclusion criterion. Patients under treatment with metformin at index date were included in the metformin group. In order to assess the possible effects of insulin treatment, a sensitivity analysis was carried out following Faillie and colleagues [19]. Patients under treatment with insulin at index date were included in the insulin group.

In our opinion, the results are broadly generalizable to primary care patients with diabetes due to the community-wide coverage of the BIFAP database. Nursing home residents are underrepresented in the database and therefore it is unknown to what extent our conclusions can be applied to this population.

In a recent cohort study using a Danish nationwide population database [26], patients who started treatment with sulfonylureas had a slightly higher risk of hospitalization for pneumonia compared to those who initiated treatment with metformin. This is in contrast with our results, though there are at least two aspects that could account for this difference. Firstly, in the Danish

study only cases of hospital-treated pneumonia were included, whereas all patients diagnosed with pneumonia were evaluated. Secondly, when assessing drug exposure, the current treatment was assessed in the present study, whereas in the Danish study patients were grouped according to their initial treatment. It is worth mentioning that as many as 60% of individuals on sulfonylureas switched to other antidiabetic drugs during the study.

Strengths

The strengths of this study include the use of a large population-based cohort with 1803 cases of CAP. The results were adjusted for more risk factors for CAP than usually described in the literature. This includes adjustment for 'time from first prescription of an oral hypoglicaemic agent', which is a relevant issue in diabetes [27]. CAP is a hard endpoint because it is associated with a significant increase in mortality and morbidity, and also has clear diagnostic criteria [28]. All cases were validated by two different researchers who were blinded to drug treatment. Conducting a case–control study nested within a well-defined cohort reduced the possibility of selection bias due to inappropriate selection of controls.

Limitations

The number of patients exposed to some antidiabetic drugs, like alpha-glucosidase inhibitors or thiazolidinediones in monotherapy was rather small. Therefore, our study was probably underpowered to detect small associations in those groups. Another aspect to be pointed out is that the results could not be adjusted by HbA1c levels, although it was adjusted for 'time since diabetes diagnosis' and 'time since first oral antidiabetic prescription'. Prescription data were used and no information about patients' adherence to treatment could be obtained. No relevant differences on this issue were expected among different groups of drugs. Also, some cases of pneumonia may be false positives (e.g., those identified exclusively by laboratory methods), but this misclassification is expected to be nondifferential by exposure. Finally, the high number of patients without recorded antidiabetic treatment at the index date could also be considered a limitation. This is probably related to weaknesses in health records, but following sensitivity analyses to assess its impact on our observations, we believe this could be considered minor.

Conclusions

In this population, no differences were observed in the incidence of CAP between the use of oral antidiabetic agents in monotherapy *vs*. metformin. In contrast, thiazolidinedione use in combination was associated with an increase in the risk of CAP when compared to metformin + sulfonylureas. The use of DPP-4 inhibitors or meglitinides in combination was not associated with an increased risk of CAP, remaining particularly uncertain because of the effect size imprecision.

Competing Interests

There are no competing interests to declare. The present study is funded by the Spanish Ministry of Health, Orden SPI/2885/2011 (trial registry number: EC11-356). The Spanish Agency of Medicines and Medical Devices (AEMPS) provided the crude data from BIFAP to the researchers according to an agreement with the Health Department of Navarre Government but did not take part in the design or in the study development. The authors are fully responsible for the analysis, results and opinions appearing in the paper and do not necessarily represent the position of the AEMPS. The views expressed are those of the authors only and do not necessarily represent the position of their respective institutions.

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Contributors

All authors are responsible for the reported research, have seen and approved the final version of the article, and have taken due care to ensure the integrity of the work. J. Gorricho, J. Garjón, M.C.C., J.E. and A.L. made substantial contributions to the conception and design of the study; J. Garjón and L.C.S. contributed to the acquisition of data; data analysis was conducted by A.A.; all authors (J. Gorricho, J. Garjón, A.A., M.C.C., L.C.S., J.E. and A.L.) took active part in the interpretation of data; the manuscript was initially drafted by J. Gorricho and was critically reviewed and subsequently approved by each co-author in its final form; J. Gorricho is the guarantor of this study.

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