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Title: Drug-induced retroperitoneal fibrosis: a case/non-case study in the French Pharmacovigilance Database

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Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

Adverse Drug Reactions

Pharmacovigilance

Pharmacoepidemiology

Drug safety

Abbreviations

ADR: adverse drug reaction

CI: confidence interval

CT: computed tomography

DEA: derivatives of ergot alkaloids

FPVD: French Pharmacovigilance Database

MedDra: Medical Dictionary for Drug Regulatory Activities

MRI: magnetic resonance imaging

RCPVs: Regional Centers of Pharmacovigilance

RF: renal failure

ROR: reporting odds ratio

RPF: retroperitoneal fibrosis

Abstract

Background: The potential role of drugs in the onset of retroperitoneal fibrosis (RPF) is poorly understood.

Aim: To identify drugs that may cause RPF.

Method: We used the case/non-case method in the French Pharmacovigilance Database (FPVD).

Results: Among the 722992 reports recorded, we identified 73 cases of RPF. 67% were men and the median age was 60 years (range 26-87). In these 73 cases, 176 drugs were ‘suspect’. Derivatives of ergot alkaloids (DEA) presented the most significant association with RPF. To a lesser extent, significant associations are found with many drugs used in cardiology —eg, beta-blockers, platelet

(TNF- α antagonist) or not known (some hypnotics, antiepileptic drugs, antipsychotics, anxiolytics, and antidepressants) to induce such an adverse drug reaction (ADR). Finally, these data could contribute to realize prospective studies to confirm these signals.

1. Introduction

Retroperitoneal fibrosis (RPF) is a rare disease characterized by a fibro-inflammatory tissue, which usually surrounds the abdominal aorta and/or the iliac arteries and extends into the retroperitoneum to envelop neighboring structures—eg, ureters (1). RPF is generally idiopathic. The clinical manifestations of RPF are nonspecific. Manifestations can be localized—eg, pain, deep vein thrombosis, leg edema (by compressive effects of the fibro-inflammatory tissue on inferior vena cava), urinary disorders until acute renal failure (by ureters compression) and/or systemic (related to the immune nature of the disease)—eg, anorexia, fatigue, fever (1–3). Because of the non-specific clinical manifestations, there is often an important delay between the first symptoms occurrence and RPF diagnosis. This explains why the diagnosis is often realized at an advanced stage of RPF especially in the context of end-stage renal failure (1). Also, these clinical manifestations are insufficient to make the diagnosis of RPF. The diagnosis is made based on computed tomography (CT) or magnetic resonance imaging (MRI) (2). Biopsy and histological examination of the retroperitoneal tissue are necessary when the mass presents atypical localizations—eg pelvic, peripancreatic and/or when the clinical signs and laboratory values suggest an infectious or malignant disease to exclude these aetiologies. Apart from surgical management such as ureterolysis, steroids are often used to treat idiopathic RPF as first-line treatment (4), also other practices in patients with relapsing RPF—eg, association with methotrexate (5), other immunosuppressants or tamoxifen—are sometimes realized.

The pathogenesis of idiopathic RPF is unclear and probably multifactorial: environmental factors (asbestos, tobacco) (6,7), systemic autoimmune process especially in the context of IgG4-related disease (8) and although thought to be small there would exist a genetic component (9). Idiopathic RPF accounts for more than two thirds of the cases of RPF. The remaining third being secondary to infections, cancer, trauma, surgery, radiotherapy or drug intake (1,10).

Iatrogenic RPF is poorly understood except for derivatives of ergot alkaloids (DEA) which represent the most common drugs associated with this adverse drug reaction (ADR). Indeed, no clear data are available about its prevalence and incidence and iatrogenic RPF is described mostly through case reports in the literature. Thus, the aim of this study was to investigate associations between drugs and reports of RPF, using the case/non-case method in the French Pharmacovigilance Database (FPVD).

2. Methods

2.1. Case/non-case method

The case/non-case method measures disproportionality between the combination of a drug and a particular ADR, here RPF, in a pharmacovigilance database (11–13). Cases are reports corresponding to the ADR of interest (here RPF) and non-cases are all reports of ADRs other than the ADR of interest. The method permits a comparison of drug exposure among cases and non-cases. The strength of the association between drug exposure and the occurrence of the ADR of interest is evaluated by the calculation of an ADR reporting odds ratio (ROR) with its 95% confidence interval (CI).

2.2. Source: the French Pharmacovigilance Database (FPVD)

The French Pharmacovigilance system consists of a network of 31 regional pharmacovigilance centers (11). The FPVD was created in 1985 to record any reports of ADR spontaneously notified by health professionals and since 2011 also by patients. For each report, information about patient (age, gender, medical history) and drug intake are recorded in the FPVD. ADRs are coded according to the

Medical Dictionary for Drug Regulatory Activities (MedDRA) (14). A causality assessment for each drug is performed using the french method (“Begaud” method) (15). Clinical details are summarized at the end of each report. Evolution can be updated later, after further investigations. Seriousness was defined as an ADR leading to death, hospitalization (or prolongation of hospitalization), persistent or significant disability or incapacity, being life-threatening or other medical justification (16).

2.3. Selection of ‘cases’ and ‘non-cases’

As a first step, we identified all spontaneous reports registered between 1 January 1985 and 27 December 2017 under the MedDra terms « peritoneal and retroperitoneal fibrosis and adhesions » (High Level Term). All these reports were carefully reviewed by 2 pharmacovigilance specialists (DB, LC). Second, we included in the study only reports with imaging confirmed RPF (CT scan or MRI). When the report was not sufficiently informative or when another aetiology was finally found (oncological, infectious) according to the detailed summary of the clinical description, the case was not included in the analysis.

‘Non-cases’ were defined as all other reports (i.e. all other reports not defined as retroperitoneal fibrosis) recorded during the same period in the FPVD.

2.4. Statistical analysis

Collected data were compared between cases (reports defined as RPF) and non-cases. We calculated the ROR to compare the risk of drug exposure among cases and non-cases. The RORs are given with their 95% CI (16).

3. Results

3.1. Characteristics of cases

Of the 722992 reports recorded in the FPVD between 1 January 1985 and 27 December 2017, 125 were reported as « peritoneal and retroperitoneal fibrosis and adhesions », 7 cases were excluded because another aetiology was finally found, 44 cases were excluded because of lack of information or RPF not confirmed by imaging and one duplicate has been identified. 73 reports were finally validated as RPF. Among them, 67% (N=49) were men. Median age was 60 years (mean: 59 years; min: 26 years; max: 87 years). Nearly half of the patients had a medical history of hypertension (45.2%; N=33), 17.8% had dyslipidaemia (N=13) and 15.1% were diabetic (N=11). 28.8% of the patients were diagnosed in a context of renal failure (RF), isolated RF or associated with lower limb damage or abdominal and/or low-back pain. A ureteral obstruction was objectified at imaging for 32.9% of patients and 6.8% had hydronephrosis. Among patients treated by antihypertensive drugs, 21% had ureteral obstruction. One patient had an aortic aneurysm and one patient had a fibrosis extended into the mediastinal zone (without details) (Table 1). Dosage of IgG4 was specified for only 4 patients: no elevation of IgG4 was found for 3 of them and one patient had a subnormal values. All cases were serious: 81% with hospitalization (N=59), 12% with “other medical justification” (N=9), 3% “persistent or significant disability or incapacity” (N=2), 3% were life-threatening (N=2) and one was fatal.

Among the 73 cases, 176 drugs were “suspect”. Median delay to RPF occurrence was 2 years and 7 months (mean: 5 years and 4 months; min: 22 days; max: 33 years and 9 months). This delay has been calculated from the date of introduction of the suspected drugs. Modification in drug intake after RPF diagnosis was known for 143 suspected drugs: drug withdrawal (N=82), unchanged dosage (N=60), decreased dosage (N=1). RPF therapeutic management was specified for 29 cases: corticosteroids (N=27) and tamoxifen (N=2). Evolution was known for only 21 cases: death (N=1), RPF extension (N=2), RPF stability (N=6), incomplete (N=11) or complete (N=1) regression.

[Table 1]

3.2. Case/non-case comparison

The case/non-case analysis included the 73 patients (“cases”) and the 722867 reports (“non-cases”). The 52 excluded cases were not included in the analysis. In the 73 cases, 176 drugs were defined as “suspect” (i.e. possibly associated with the occurrence of ADR whatever the level of imputability), with a mean of 2.4 drugs per case. Table 2 indicates the values of ROR between the occurrence of RPF and drug exposure in the FPVD. Derivatives of ergot alkaloids (DEA) presented the most significant association with RPF. To a lesser extent, significant association was found with many drugs used in cardiology —eg, beta-blockers, platelet antiaggregant, statins, antihypertensive drugs including inhibitors of the renin-angiotensin system and diuretics, drugs used in neuropsychiatry—eg, hypnotics, antiepileptic drugs, anxiolytics, antipsychotics, and antidepressants and with others therapeutics class—eg TNF-alpha, antidiabetics... Concerning beta-blockers, when the indication was known, it was always hypertension except for one case where the indication was myocardial infarction with a probable heart failure.

[Table 2]

4. Discussion

As far as we know, this is the first large systematic study that investigates drugs involved in RPF and the characteristics of iatrogenic RPF through a pharmacovigilance database. Previously, RPF has been acknowledged mainly by case reports (Table 3). Our study suggests that, in usual medical practice, many drugs, not only DEA, can be suspected in RPF occurrence.

The case/non-case method is a relevant method for detecting associations between a rare adverse drug effect such as RPF and drug exposure in real conditions of use. This study presents some mandatory methodological drawbacks as with all other studies using a pharmacovigilance database —eg, underreporting (17,18) and other biases detailed below. From a methodological point of view, our study is original compared with previous publications about iatrogenic RPF. It improve our knowledge about the circumstances of occurrence of this rare ADR in real clinical practice.

Epidemiological characteristics of iatrogenic RPF are not established in literature. Compared to patients with idiopathic RPF, the characteristics of our cases were similar in terms of age or sex ratio. Men are approximately affected twice as often as women by RPF (1,19). The mean age is around 50-60 years (1,19). Nearly half of our patients suffering from hypertension which corresponds to the proportion described by Estrade and *al.* (3). Hypertension in patients with RPF is probably of renal origin by a rise in renin release secondary to urinary tract obstruction or entrapment of the renal artery (20). The considerable delay between the suspected drug introduction and RPF diagnosis can be explained by the nonspecific clinical manifestations of the disease and by the slow chronic process of fibrosis. Lugosi and *al.* found a mean delay between the first symptoms and the diagnosis of 258 days with extremes ranging from one to 1422 days (21). RPF evolution is variable: complete or partial regression, persistence or extension despite corticosteroid therapy (3,21), which is found in our study.

We found a very important disproportionality signal with DEA that can be explained partly by a notoriety bias. Indeed, DEA including antiparkinsonian drugs, inhibitors of prolactin secretion and antimigraine drugs, is the pharmacological class most frequently associated with iatrogenic RPF in literature (22,23) with a fibrotic risk widely described in valvular heart disease (24–26). The pharmacological explanation is that DEA induced activation of the 5-HT_{2B} serotonin receptor, lead to fibroblast proliferation and increased extracellular matrix, including collagen and glycosaminoglycan (25,27).

The association between beta-blockers and RPF is currently not well established. Various cases were published in the 70s-80s (28–30). Some authors suggested that beta-blockers were probably being used to treat hypertension associated with RPF rather than to induce directly RPF (31). Indeed,

hypertension induced by RPF is probably diagnosed and treated by antihypertensive drugs before the underlying disease diagnose. The hypothesis of a protopathic bias (and also a notoriety bias, for the same reasons than DEA) could explain the important signal found with beta-blockers and especially because beta-blockers indication in our study is always hypertension excepting for one patient with a medical history of myocardial infarction and probable heart failure. However, in our study patients treated by antihypertensive drugs including beta-blockers were not more affected by ureteral obstruction. This doesn't support the protopathic bias hypothesis. A significant disproportionality was also found with other antihypertensive drugs—eg diuretics, agents acting on the renin-angiotensin system and lipid-modifying agents, platelet antiaggregants and antidiabetic drugs. Except for some cases described in the 70s-80s with prolonged treatment of an analgesic dose of aspirin (32) and a case reported with hydrochlorothiazide (33) there is no association between these drugs and RPF occurrence in literature. It's should be noted that benfluorex has a known risk of valvular lesions explained by 5-HT_{2B} serotonin receptor activation by one of its metabolites, norfenfluramine. Lugosi and *al.* describe that near than half patients with RPF have at least two cardiovascular risk factors (21) that could explain the use of these drugs in patients with RPF even if the absence of a significant signal found with calcium antagonists limits this hypothesis.

According to current data available in the literature, the role of TNF- α antagonist in RPF genesis is not clear. Some cases are described, mainly with etanercept (34–36). Occurrence of a pathology for which a treatment is known to be effective called a paradoxical effect, has been notified for TNF- α antagonist—eg sarcoidosis (37), psoriasis, scleritis, uveitis, large-vessel vasculitis, and inflammatory bowel diseases. Lupus-like syndrome is also reported with these drugs. This dysregulation of the immune system induced by TNF- α antagonists could promote immune-mediated RPF occurrence. Less likely, RPF might be a manifestation of a systemic autoimmune or inflammatory disease (1) treated by TNF- α antagonist with therefore a possible indication bias. Moreover, we found a case of refractory RPF to combined glucocorticoid and methotrexate therapy treated effectively with infliximab (38).

A significant disproportionality was found with antihistamines drugs, ferrous sulfate and various drugs used in neuropsychiatry such as antipsychotics, antiepileptics, hypnotics, anxiolytics, and antidepressants. According to our knowledge, there is no association between these drugs and RPF in literature. It is therefore difficult to conclude about a new association between the occurrence of RPF and these drugs brought to light in this study or on the existence of unidentified biases. There is also no pharmacological explanation that could explain this signal. More generally about fibrotic risk, currently data shown that elevation of serotonin blood and/or synaptic cleft concentrations resulting from the pharmacological effects of antidepressant is not sufficient to increase the fibrotic risk and that 5-HT_{2B} serotonin receptor stimulation seems to be the main factor (39). None of these drugs have a significant 5-HT_{2B} agonist activity and further studies are needed to understand this signal.

Some authors in the 70s-80s suggested that excessive and prolonged consumption of analgesics (codeine, aspirin, phenacetin) could be associated with the occurrence of RPF (32). In our study, there is no significant signal found with analgesics apart from aspirin.

No significant signal was found with proton pump inhibitors, platinum salts or calcium antagonists.

[Table 3]

5. Conclusion

In conclusion, the association between RPF occurrence and drugs is difficult to establish because of a history of drug intake sometimes arduous to reconstitute due to late diagnosis and difficulty to conclude on the evolution at the suspected drug withdrawal (unsystematic regression of fibrosis or potentially related to corticosteroids efficacy). Despite the compulsory limits of the case/non-case study

(confounding factors, underreporting...), these data represent a pharmacovigilance signal and can contribute to perform prospective studies in order to confirm these signals. A significant association has been found between various drugs and RPF reports. This concerns not only drugs known to be associated with this ADR (DEA) but also other drugs less known (TNF- α antagonist) or not known (some antipsychotics, antiepileptics, hypnotics, anxiolytics, and antidepressants) to induce such an ADR. Our results emphasize that, in clinical practice, a systematic anamnesis about drug intake should be performed in each aetiological research of RPF and especially because no aetiology is found for more than two-thirds of the cases of RPF.

6. Declaration of interests

All authors have no conflict of interest to disclose in relation to this study.

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Localization of fibrosis on imaging, N (%)	WP	UO	UO+FK	UO+H	M	AA	Total
Circumstances of diagnostic, N (%)							
Isolated RF	6 (8.2)	6 (8.2)	1 (1.4)	2 (2.7)	1 (1.4)	0 (0)	16 (21.9)
Isolated LLD	5 (6.8)	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)	6 (8.2)
Pain*	16 (21.9)	4 (5.5)	0 (0)	0 (0)	0 (0)	1 (1.4)	21 (28.8)
RF and LLD	1 (1.4)	2 (2.7)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4.1)
RF and pain*	0 (0)	2 (2.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.7)
LLD and pain*	1 (1.4)	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)	2 (2.7)
FD	4 (5.5)	2 (2.7)	0 (0)	0 (0)	0 (0)	0 (0)	6 (8.2)
NS	14 (19.2)	2 (2.7)	0 (0)	1 (1.4)	0 (0)	0 (0)	17 (23.3)
Total	47 (64.4)	18 (24.7)	1 (1.4)	5 (6.8)	1 (1.4)	1 (1.4)	73 (100)
Total RF (isolated or associated with pain or LLD)	7 (9.6)	10 (13.7)	1 (1.4)	2 (2.7)	1 (1.4)	0 (0)	21 (28.8)
Total LLD (isolated or associated with pain or RF)	7 (9.6)	2 (2.7)	0 (0)	2 (2.7)	0 (0)	0 (0)	11 (15.1)
Total 'pain' (isolated or associated with LLD or RF)	17 (23.3)	6 (8.2)	0 (0)	1 (1.4)	0 (0)	1 (1.4)	25 (34.2)

RF: renal failure
LLD: lower limb damage (edema or deep vein thrombosis)
 *abdominal and/or low-back pain
FD: fortuitous diagnosis
NS: circumstances of diagnostic are not specified

WP: without particularities. RPF with involvement of abdominal aorta and/or vena cava and/or iliac arteries and/or renal arteries and/or mesenteric arteries without specific mention about involvement of urinary tract, kidneys or mediastinal zone or aortic aneurysm.
UO: ureteral obstruction
FK: fibrosis surrounding kidneys
H: hydronephrosis
M: involvement of mediastinal zone (without details)
AA: aortic aneurysm

Table 1: Circumstances of diagnostic and the localization of fibrosis on imaging (n=73)

Therapeutic Class	Number of RPF in the FPVD	Total number of cases (all ADR included)	ROR	95% CI
Beta blockers	28	11446	38,8	(24.2, 66.2)
acebutolol	3	1269	24,4	(7.7, 77.7)
atenolol	5	1800	29,5	(11.9, 73,3)
betaxolol	1	232	43,5	(6.0, 314.0)
bisoprolol	9	3162	32,1	(16.0, 64.6)
celiprolol	2	563	36,3	(8.9, 148.2)
metoprolol	1	614	16,4	(2.3, 118.0)
nadolol	1	153	66	(9.1, 478.3)
nebivolol	1	912	11	(1.5, 79.3)
pindolol	1	164	61,6	(8.5, 445.8)
propranolol	3	1708	18,1	(5.7, 57.6)
sotalol	1	869	11,6	(1.6, 83,2)
Diuretics	11	27259	4,5	(2.4, 8.6)
loop diuretics	1	9329	1,1	(0.1, 7.6)
furosemide	1	9329	1,1	(0.1, 7.6)
potassium-sparing diuretics	3	5595	5,5	(1.7, 17.5)
spironolactone	2	5031	4	(1.0, 16.4)
triamterene	1	564	17,8	(2.5, 128.5)
thiazide diuretics	7	12335	6,1	(2.8, 13.3)
altizide	2	1876	10,8	(2.7, 44.2)
clopamide	1	26	401,6	(53.7, 3003.7)
cyclothiazide	1	237	42,5	(5.9, 307.3)
hydrochlorothiazide	2	7794	2,6	(0.6, 10.5)
indapamide	1	2402	4,2	(0.6, 30.0)
Hypolipidemic drugs	8	9706	9,1	(4.3, 18.9)
statin	6	7480	8,6	(3.7, 19.8)
rosuvastatin	2	1632	12,5	(3.1, 50.9)
fluvastatin	1	524	19,2	(2.7, 138.3)
pravastatin	1	2473	4	(0.6, 29.1)
simvastatin	2	2851	7,1	(1.7, 29.0)
fibrate drugs	1	2083	4,8	(0.7, 34.6)
fenofibrate	1	2083	4,8	(0.7, 34.6)
other	1	143	70,7	(9.8, 512.2)
cholestyramine	1	143	70,7	(9.8, 512.2)
Agents acting on the renin-angiotensin system	7	16458	4,6	(2.1, 9.9)
angiotensin II receptor antagonists	3	6055	5,1	(1.6, 16.1)
irbesartan	1	2182	4,6	(0.6, 33.0)
losartan	1	1366	7,3	(1.0, 52.9)
valsartan	1	2507	4	(0.6, 28.7)
angiotensin-converting-enzyme inhibitors	4	10403	4	(1.4, 10.9)
ramipril	1	3725	2,7	(0.4, 19.3)
perindopril	2	3927	5,2	(1.3, 21.0)
enalapril	1	2751	3,6	(0.5, 26.2)

Therapeutic Class	Number of RPF in the FPVD	Total number of cases (all ADR included)	ROR	95% CI
Calcium antagonists	3	10505	2,9	(0.9, 9.2)
nitrendipine	1	5045	2	(0.3, 14.2)
amlodipine	1	3527	2,8	(0.4, 20.4)
nicardipine	1	1933	5,2	(0.7, 37.3)
Antiarrhythmic drugs	2	4210	4,8	(1.2, 19.6)
amiodarone	1	487	20,6	(2.9, 148.9)
digoxine	1	3723	2,7	(0.4, 19.3)
Antipsychotic drugs	7	12100	6,2	(2.9, 13.6)
haloperidol	2	2610	7,8	(1.9, 31.7)
zuclopenthixol	1	546	18,4	(2.6, 132.7)
cyamemazine	1	3779	2,6	(0.4, 19.0)
levomepromazine	1	1459	6,9	(1.0, 49.5)
risperidone	1	3419	2,9	(0.4, 21.0)
pipamperone	1	287	35,1	(4.9, 253.4)
Anxiolytic drugs	6	9448	6,8	(2.9, 15.6)
bromazepam	2	3847	5,3	(1.3, 21.5)
alprazolam	2	3297	6,2	(1.5, 25.1)
meprobamate	2	2304	8,8	(2.2, 36.0)
Hypnotic drugs	8	8496	10,4	(5.0, 21.6)
aceprometazine	2	1633	12,5	(3.1, 50.8)
zolpidem	5	3771	14	(5.7, 34.8)
zopiclone	1	3092	3,2	(0.4, 23.3)
Antimigraine drugs	16	1576	129,8	(74.4, 226.5)
dihydroergotamine	7	600	129,2	(59.0, 282.7)
ergotamine	1	899	11,2	(1.6, 80.4)
methysergide	8	77	1289,4	(596.2, 2788.5)
Antidepressants	8	21315	4,1	(1.9, 8.4)
serotonin selective reuptake inhibitors	3	10083	3	(1.0, 9.6)
sertraline	1	1656	6,1	(0.8, 43.6)
fluoxetine	1	3853	2,6	(0.4, 18.7)
paroxetine	1	4574	2,2	(0.3, 15.7)
serotonin-norepinephrine reuptake inhibitors	1	3100	3,2	(0.4, 23.2)
venlafaxine	1	3100	3,2	(0.4, 23.2)
tricyclic antidepressant	3	5712	5,4	(1.7, 17.1)
amitriptylline	1	2701	3,7	(0.5, 26.7)
maprotiline	1	431	23,3	(3.2, 168.3)
clomipramine	1	2580	3,9	(0.5, 27.9)
other antidepressant	1	2420	4,1	(0.6, 29.8)
mianserine	1	2420	4,1	(0.6, 29.8)
Antiepileptic drugs	5	6813	7,7	(3.1, 19.2)
valproic acid	4	4274	9,8	(3.6, 26.7)
lamotrigine	1	2539	3,9	(0.5, 28.4)

Therapeutic Class	Number of RPF in the FPVD	Total number of cases (all ADR included)	ROR	95% CI
Antiparkinsonian drugs	3	3440	9	(2.8, 28.5)
trihexyphenidyl	1	944	10,6	(1.5, 76.6)
pergolide	1	194	52	(7.2, 376.2)
levodopa, carbidopa	1	2302	4,3	(0.6, 31.3)
Inhibitors of prolactin secretion	4	1148	36,6	(13.3, 100.4)
cabergoline	1	143	70,7	(9.8, 512.2)
bromocriptine	3	1005	30,9	(9.7, 98.2)
Non-steroidal anti-inflammatory drugs	4	13931	3	(1.1, 8.1)
diclofenac	1	4532	2,2	(0.3, 15.9)
celecoxib	1	1528	6,6	(0.9, 47.3)
ibuprofen	1	6744	1,5	(0.2, 10.6)
glafenine	1	1127	8,9	(1.2, 64.1)
Analgesics (except anti-inflammatory)	2	32826	0,6	(0.15, 2.41)
tramadol	1	8383	1,2	(0.2, 8.5)
acetaminophen	1	24443	0,4	(0.1, 2.9)
Antidiabetic drugs	6	18129	3,5	(1.5, 8.0)
benfluorex	2	12002	1,7	(0.4, 6.8)
gliclazide	1	1445	6,9	(1.0, 50.0)
metformine	3	4682	6,6	(2.1, 20.9)
Platelet antiaggregants	7	8294	9,1	(4.2, 19.9)
ticlopidine	1	1573	6,4	(0.9, 45.9)
aspirin	5	6183	8,5	(3.4, 21.2)
dipyridamole	1	538	18,7	(2.6, 134.7)
TNF-α antagonist	4	4614	9	(3.3, 24.8)
adalimumab	2	2507	8,1	(2.0, 33.0)
etanercept	2	2107	9,6	(2.4, 39.4)
Platinum salts	2	6493	3,1	(0.8, 12.7)
carboplatin	1	3372	3	(0.4, 21.3)
cisplatin	1	3121	3,2	(0.4, 23.1)
Antihistamines drugs	2	1763	11,5	(2.8, 47.1)
alimemazine	1	1567	6,4	(0.9, 46.1)
doxylamine	1	196	51,5	(7.1, 372.3)
Proton pump inhibitors	2	15083	1,3	(0.3, 5.4)
omeprazole	1	10180	1	(0.1, 7.0)
esomeprazole	1	4903	2	(0.3, 14.6)

Therapeutic Class	Number of RPF in the FPVD	Total number of cases (all ADR included)	ROR	95% CI
Other drugs	31			
timolol eye drop	3	726	42,8	(13.4, 136.3)
levothyroxine	2	27616	0,7	(0.2, 2.9)
ferrous sulfate	2	1576	12.9	(3.2, 52.7)
alendronate	1			
alfuzosin	1			
allopurinol	1			
avocado soy unsaponifiables	1			
caffeine	1			
clobenzorex	1			
finasteride	1			
fluindione	1			
fluorouracil	1			
horse chestnut extract	1			
insulin	1			
interferon B1b	1			
latanoprost eye drop	1			
memantine	1			
oxymetazoline	1			
paclitaxel	1			
pentaerythryl	1			
permethol	1			
ponatinib	1			
tamsulosin	1			
travoprost eye drop	1			
trimebutine	1			
sibutramine	1			
yohimbine	1			
Total	176			
DEA*	21	2918	100,4	(60.4, 166.8)
benzodiazepines or benzodiazepine-like agents **	10	14007	8	(4.1, 15.7)

*cabergoline n=1, bromocriptine n=3, pergolide n=1, dihydroergotamine n=7, ergotamine n=1, methysergide n=8

**bromazepam n=2, alprazolam n=2, zolpidem n=5, zopiclone n=1

ROR was not calculated when N=1 and no possibility of grouping by pharmacological class.

Disproportionality signals appear in bold.

Table 2: Risk of exposure to drugs in cases (n = 73 with 176 suspect drugs) and noncases (n = 722867) and occurrence of RPF in the French Pharmacovigilance Database (FPVD)