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ORIGINAL INVESTIGATION

A comparative study of QT prolongation with serotonin reuptake inhibitors

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Abstract
Background QT interval prolongations were described with citalopram and escitalopram. However, the effects of the other serotonin reuptake inhibitors (SRIs) remained discussed. In order to identify a putative signal with other SRIs, the present study investigates the reports of QT interval prolongation with SRIs in two pharmacovigilance databases (PVDB).
Methods Two kinds of investigations were performed: (1) a comparative study in VigiBase®, the WHO PVDB, where notifications of QT prolongation with six SRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) were selected. Cases with overdose or pregnancy were excluded. The relationship between the "suspected" SRI and occurrence of QT prolongation was assessed by calculating reporting odds ratio (ROR) in a case/non-case design. (2) A descriptive study of QT prolongation reports with citalopram and escitalopram in the French FPVD.
Results In VigiBase®, 855 notifications were identified (mean age 56.2 years, mainly women 73%). Among them, 172 (20.1%) were associated to escitalopram; 299 (35.0%), to citalopram; 186 (21.8%), to fluoxetine; 94 (11.0%), to sertraline; 66 (7.7%), to paroxetine; and 38 (4.4%) to fluvoxamine. A significant ROR value (higher than 1) was only found for citalopram (3.35 CI95% [2.90–3.87]) or escitalopram (2.50 [2.11–2.95]). In the FPVD, eight reports of QT prolongation were found with citalopram and 27 with escitalopram, mainly in women (77.1%) with a mean age of 73.2 years. In 23 cases (66%), SRIs were associated with other suspected drugs, mainly cardiotropic or psychotropic ones. Hypokalemia was associated in six patients.
Conclusion This study, performed in real conditions of life, shows a clear signal of QT prolongation with only two SRIs, citalopram and escitalopram, indicating that QT prolongation is not a SRI class effect.

Keywords QT interval · Antidepressants · Serotonin reuptake inhibitors · Citalopram · Escitalopram

Introduction

Since their launch in the 1980s, serotonin reuptake inhibitors (SRIs) have rapidly taken a large place in the pharmacological management of major depressive episodes and anxiety disorders. They are currently considered as first-line antidepressant drugs by international recommendations and guidelines (Anderson 2000). This conclusion is not related to a better efficacy compared to older antidepressants like imipraminics (tricyclic antidepressants, TCA), but to a potential lower risk of adverse drug reactions (ADRs) (Anderson 2000).

From 2011, a controversy about the potential effects of SRIs on QT interval has emerged. In fact, some post-marketing reports of QT lengthening and torsades de Pointes led Food and Drug Administration (FDA) to perform a cross-over randomized study in healthy volunteers to assess the effects on QTc of citalopram and its S-isomer, escitalopram. This study found a dose-dependent lengthening of QTc interval up to 18.5 and 10.7 ms with 60 mg citalopram and 30 mg escitalopram, respectively (FDA Drug Safety Communication

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n.d.-a). Consequently, FDA sent a first warning in 2011 recommending citalopram doses no greater than 40 mg daily in adults followed by a second warning in 2012 with no more than 20 mg daily in patients older than 60 years (FDA Drug Safety Communication n.d.-a; FDA Drug Safety Communication n.d.-b). In patients with hepatic or impairment, with a slow metabolizer phenotype by cytochrome CYP 2C19 or patients taking concomitant cimetidine or another CYP 2C19 inhibitor, the maximal dose was reduced to 20 mg daily (FDA Drug Safety Communication n.d.-b). It was also proposed to limit the daily dose of escitalopram to 10 mg in the elderly (FDA Drug Safety Communication n.d.-b). Following these warnings, Rector's group (Rector et al. 2016) showed, in a Veteran population previously treated with high dosages of citalopram, that dosage reduction was associated with a higher rate of hospitalization than that observed before dosage reduction, underlining potential unintended clinical consequences of such decisions.

Although additional cross sectional studies found QT prolongation with citalopram and escitalopram (Castro et al. 2013; Girardin et al. 2013), several other data are conflicting and the discrepancies between the studies are mainly on clinical outcomes: for example, a cohort study, using Veterans Health Administration data between 2004 and 2009, failed to find an elevated risk of ventricular arrhythmia or all-cause, cardiac or non-cardiac, mortality associated with citalopram or sertraline (Zivin et al. 2013). In another cohort study, using 1999–2003 Medicaid claims and investigating the risk of sudden death and ventricular arrhythmia with 20 antidepressants, only mirtazapine was associated to a significant risk (Leonard et al. 2011). The recent study from the QResearch primary care database investigating the relation between antidepressants over a 5-year follow-up period of exposure, failed to identify a significant association between cardiovascular risks including arrhythmia and the use of antidepressant drugs in general, citalopram in particular. Interestingly, in this study, results indicated that fluoxetine could protect against cardiovascular events, including arrhythmias (Coupland et al. 2011).

Thus, these major discrepancies led us to perform a study in VigiBase®, the WHO pharmacovigilance database (PVDB) to compare QT interval augmentations in patients receiving SRIs. In order to try to define the main clinical characteristics of this ADR, we also described data registered with citalopram and escitalopram in the French PVDB (FPVDB).

Methods

Data source

Two PVDB were used for this study.

First, VigiBase®, the WHO global individual case safety report (ICSR) database system which contains more than 14 million reports of ICSRs (ADRs) received from 120 countries members worldwide since 1968 (Bate et al. 2008). ICSRs' data include administrative information (country, type of report, qualification of reporter), patient data (gender, age), characteristics of the reported ADR (description with MedDRA terms [Medical Dictionary for Regulatory Activities], date of onset reaction, outcome, WHO assessment causality), and drug (s) involved (name, drug start and stop dates, time to onset, indication, dechallenge, rechallenge). Level of completeness of information is also included. Each ADR is characterized as a "serious" or "non serious" according to WHO definition, with a serious ADR leading to death or life-threatening or triggering hospitalization (or prolongation of existing hospitalization) or leading to persistent incapacity or disability or judged clinically relevant by the physician reporting the case (Edwards and Aronson 2000).

Second, the FPVDB, which registers all ADRs notified to the French pharmacovigilance network (including 31 regional centers) from 1984. The reporting of serious or "unlabelled" ADRs has been compulsory in France since 1984. For each ADR report, information about patient, ADR, and drug exposure are recorded (Vial 2016). Reports are evaluated according to the French method of causality assessment (Miremont-Salamé et al. 2016).

Comparative study in VigiBase®

QT prolongation cases were defined according to the MedDRA preferred terms (PTs), "Electrocardiogram QT prolonged" using the System Organ Class (SOC) classification. Drug exposition was identified according to Anatomical Therapeutic and Clinical (ATC) classification by the presence in the report of one of the six SRIs of interest (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, ATC code N06AB) defined as suspected and whatever the level of causality assessment (Miremont-Salamé et al. 2016). For each case, demographic data, seriousness, and outcome were registered. Drug doses were not included in this study since they are not exhaustively registered in VigiBase®. After full review of all the suspected reports, cases with pregnancy, unknown gender or age, several SRIs, overdose, and congenital QT were excluded. Cases of overdoses were also excluded since occurrence of QT prolongation is well known in such circumstances whatever the SRI, and it was not the purpose of the study to study QT prolongation in overdose reports. ICSRs were included whatever the country of origin. We used a case/non-case design measuring disproportionality of combination between a drug and a particular ICSR: reports containing QT prolongation (LLT term) were cases and all other reports without QT prolongation non-cases. Thus, a disproportionality analysis was performed using cases and non-cases allowing to calculate reporting odds ratios (RORs), as previously described (Montastruc et al. 2011).

Using the same criteria, we also selected reports with methadone, a drug well known to induce QT prolongation (Perrin-Terrin et al. 2011; Frauger et al. 2017), as a positive control in our study.

Descriptive study in the FPVDB

Reports of QT prolongation registered from 1984 with citalopram or escitalopram were selected using the key word "QT interval prolonged" (PT term). In this descriptive part of the study, only reports with an imputation score values ≥ I1 "possible" [according to the French method (Miremont-Salamé et al. 2016)] were included. As previously, reports with overdose, pregnancy, unknown gender or age, several SRIs, and congenital QT were excluded after full medical and pharmacological review of all the suspected reports. For each report, age, gender, involved SRI, and its dosage, associated with suspected drugs, delay of occurrence, medical cardiac history, seriousness, outcome (recovered, not recovered, unknown), and QT (and QTc if available) values were registered.

Statistical analysis

A descriptive analysis of the population was first carried out. Quantitative variables were expressed as mean value (± standard deviation and range). Qualitative variables were shown in numbers and percentages. Secondary, the relationship between the six SRIs and occurrence of QT prolongation was assessed by calculating RORs with their 95% confidence interval (95% CI) in the case non-case analysis (Montastruc et al. 2011). ROR were adjusted on gender and age. All analyses were performed using SAS® software, version 9.4 (SAS Institute. Inc., Cary. NC, USA). Statistical significance was defined as a p threshold of 0.05.

Results

Comparative study in VigiBase®

Among the 246,204 ICSRs related to the six SRIs, 855 (0.3%) were QT prolongations according to selection criteria. They involved mainly women (73%), mean age 56.2 ± 21.3 years. One hundred seventy-two (20.1%) were associated to escitalopram; 299 (35.0%), to citalopram; 186 (21.8%), to fluoxetine; 94 (11.0%), to sertraline; 66 (7.7%), to paroxetine; and 38 (4.4%), to fluvoxamine. ICSRs were mainly considered as serious (92.7%) with 23 deaths (Table 1).

Figure 1 shows that citalopram and escitalopram (but not the other SRIs) were associated with a significant ROR value (higher than 1). The ROR value for methadone (selected as a positive control) was 32.9 (95% CI 29.7–36.3) ($p < 0.0001$).

Table 1 Characteristics of the 855 individual case safety reports (ICSRs) of QT prolongation with six SRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) registered in VigiBase®

Characteristics	VigiBase® (N = 855)
Female, *n* (%)	620 (72.5%)
Age, mean ± SD [min-max]	56.2 ± 21.3 [0.0003*–95]
Seriousness of the ADR, *n* (%)	
Serious	632 (92.7%)
Death	23 (3.6%)
Hospitalization	261 (41.3%)
Life threatening	117 (18.5%)
Others	225 (35.6%)
Unknown	6 (0.9%)
Non serious	50 (7.3%)
Completeness score, mean ± SD [min-max]	0.5 ± 0.2 [0–1]

SD standard deviation, *min* minimum, *max* maximum

*2 h of life

Descriptive study in the FPVDB

The results obtained in VigiBase® with citalopram and escitalopram led us to investigate the main characteristics of this ADR in the FPVDB, which is a medically and pharmacologically validated database (Vial 2016). In the FPVD, 72 notifications with QT lengthening were found (mean age 69.7 ± 15.1 years, mainly women 77.8%), i.e., 27 (38.0%) with escitalopram, 8 (11.0%) with citalopram, and the remaining 37 cases with the other SRIs. Table 2 shows the main characteristics of the 35 cases of QT prolongation with citalopram (dose in all cases 20 mg) and escitalopram (mean dose 11.7 ± 6.4 mg, range 5.0–20.0 mg). QT prolongation occurred mainly in women (77%). Mean age was

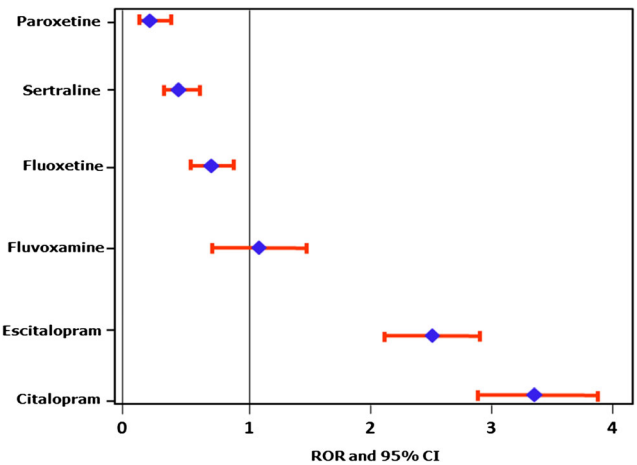

Fig. 1 Reporting odds ratio (ROR) of QT prolongation in the 855 patients receiving SRIs in VigiBase®. The ROR values were adjusted on gender and age and are given with their 95% confidence interval. Statistical significance was defined as a p threshold of 0.05

Table 2 Main characteristics of the 35 reports of QT prolongation found in the French Pharmacovigilance Database with citalopram (n = 7) or escitalopram (n = 28)

N	Age	Gender	Drug	Dose	Associated suspected drug (s)	Delay of occurrence	Medical cardiac history	Serious	Outcome	QT value (ms)
1	85	F	Citalopram	20 mg	Disopyramide, hydroxyzine, risperidone, spironolactone	U	Supraventricular arrhythmias	YES	R	QTc = 530
2	74	F	Citalopram	20 mg	None	21 D	Myocardial infarction	NO	R	–
3	76	F	Citalopram	U	Furosemide, levothyroxine, j ramipril	3 Y	Myocardial infarction, atrial fibrillation	YES	NR	QTc = 480
4	89	F	Citalopram	U	Nebivolol	U	Phlebitis	YES	R	–
5	65	F	Citalopram	20 mg	None	U	Angor	YES	R	–
6	81	F	Citalopram	20 mg	Olanzapine	10 D	None	YES	R	QTc = 460
7	68	F	Citalopram	20 mg	Digoxine, amiodarone	U	Atrial fibrillation	YES	R	–
8	70	M	Citalopram	20 mg	Cyamemazine	7 D	None	NO	R	QTc = 493
9	77	F	Escitalopram	10 mg	Aliskiren, amiodaron, domperidone	U	Atrial fibrillation	YES	R	QT = 600
10	40	F	Escitalopram	20 mg	Cyamemazine, dextropropoxyphene	7 D	None	YES	R	–
11	77	F	Escitalopram	5 mg	Bisoprolol	U	Myocardial infarction, atrial fibrillation	YES	NR	–
12	61	F	Escitalopram	20 mg	Bilastine, hydroxyzine	U	None	YES	R	QTc = 600
13	84	F	Escitalopram	5 mg	Bisoprolol	81 D	Myocardial infarction	NO	NR	QTc = 506
14	50	F	Escitalopram	20 mg	None	5 Y	Myocardial infarction, dyslipidemia, arterial hypertension	NO	NR	QTc = 550
15	86	F	Escitalopram	U	None	U	None	YES	R	QT = 485
16	67	F	Escitalopram	U	Indapamide, sotalol, benzoic acid	U	Atrial fibrillation	YES	Death	–
17	81	F	Escitalopram	20 mg	None	2 M	None	YES	R	–
18	81	F	Escitalopram	5 mg	Bisoprol	10 D	Phlebitis	YES	R	QTc = 444
19	38	F	Escitalopram	5 mg	None	5 M	Familial bradycardia	YES	R	QT = 500
20	71	F	Escitalopram	20 mg	None	32 D	Myocardial infarction	YES	R	QTc = 520
21	78	F	Escitalopram	U	Amiodarone	SD	Atrial fibrillation	YES	R	QT = 630
22	85	F	Escitalopram	10 mg	None	4 M	Myocardial infarction, Arterial hypertension	YES	R	–
23	66	F	Escitalopram	U	None	8 M	None	NO	NR	–
24	54	F	Escitalopram	10 mg	None	4 Y	Myocardial infarction	NO	R	QTc = 570
25	87	F	Escitalopram	5 mg	None	U	Atrial fibrillation	YES	R	
26	56	F	Escitalopram	5 mg	Candesartan, ivabradine, spironolactone	U	Congestive cardiomyopathy, mitral insufficiency	YES	R	QTc = 500
27	85	F	Escitalopram	10 mg	Galantamine, irbesartan, diuretic, paracetamol	U	Atrial fibrillation, paroxystic tachyardia	YES	R	QTc = 670
28	75	F	Escitalopram	20 mg	Bisoprolol, furosemide	> 6 M	Bentall surgery	YES	R	QTc = 640
29	65	M	Escitalopram	10 mg	Pramipexole	16 D	None	YES	R	–
30	82	M	Escitalopram	20 mg	Amiodarone, flecainide	U	Atrio ventricular block, hypertensive cardiomyopathy	YES	R	QT = 800
31	86	M	Escitalopram	U	Digoxine	U	None	YES	R	–
32	94	M	Escitalopram	10 mg	None	U	None	YES	R	–
33	87	M	Escitalopram	5 mg	Alimemazine	U	Mitral insufficiency	YES	R	QTc = 526
34	80	M	Escitalopram	10 mg	Amiodarone	3 D	Myocardial infarction, atrial fibrillation	YES	R	QT = 480
35	61	M	Escitalopram	U	Diazepam, metoclopramide	U	Myocardial infarction	YES	R	QTc = 640

U unknown value, *R* recovered, *NR* not recovered, *M* months, *D* days, *Y* years, *SD*: some days

73.2 ± 13.7 years (38–94). Most of the cases (n = 29; 83%) were serious. Delay of occurrence varied from 3 days to several years after SRI introduction. In 23 cases (66%), citalopram or escitalopram was associated with other suspected drugs, mainly amiodarone, beta-blocking agents, diuretics, and/or dopamine antagonists… However, QT prolongation occurred in ten cases with one SRI alone (n = 2 for citalopram; n = 8 for escitalopram). In 23 cases (66%), a significant previous medical history (mainly cardiac disease) was also found. Hypokalemia was associated in 6 out of the 35 patients. Evolution was favorable in most cases, except one death (from a cardiac arrest) in a 67-year-old woman with a previous history of atrial fibrillation. Mean reported value of QT were 582 ms (480–800, n = 6) and QTc 541 ms (444–670, n = 15). Causality assessment was possible (I1) in 17 reports (5 citalopram, 12 escitalopram), "plausible" (I2) in 16 reports (3 citalopram, 13 escitalopram), and "likely" (I3) in 2 reports with escitalopram.

Discussion

The present study was performed to investigate in real conditions of life a putative signal of QT prolongation with the different SRIs since the available published data are conflicting. For this purpose, we applied a validated method for relatively rare signals, the case non-case one, in the largest PVDB in the world VigiBase® including more than 14 million reports. After finding a signal for only citalopram and escitalopram, we decided to use the FPVDB to clinically describe the main characteristics of QT prolongation ADRs with these two SRIs.

The main finding of this study was the signal described with citalopram and escitalopram. In fact, as described above, published results are confusing. Besides studies discussed above (Castro et al. 2013; Girardin et al. 2013; Zivin et al. 2013; Leonard et al. 2011; Coupland et al. 2011), other published papers show divergent results. For example, the Danish case-time-control study investigating the risk of out-of-hospital cardiac arrest with antidepressants found a comparable risk with TCAs and SRIs, without any association for serotonin-norepinephrine reuptake inhibitors. In this study, there was an association with nortriptyline and citalopram but not escitalopram (Weeke et al. 2012). A systematic search of primary literature and case reports found ADR reports with escitalopram but not with other SRIs (Funk and Bostwick 2013). Beach's meta-analysis found a significant greater QTc increase with TCAs than with SRIs and, among SRIs, a greater QTc prolongation with citalopram than with other SRIs (Beach et al. 2014). Finally, the population-based Rotterdam Study found that, among SRIs, the more important increase in QTc values were found with citalopram. The authors also concluded that other SRIs may not give a clinically relevant QTc prolongation (Maljuric et al. 2015). Our data offer new interesting results in the real conditions of life allowing to describe an association between QT prolongation and only two SRIs.

The results obtained in Vigibase® led us to use the FPVDB to describe the main clinical characteristics of this ADR. In fact, this kind of descriptive approach is useful since QT prolongation with SRIs is a relatively rare ADR (Funk and Bostwick 2013; Aström-Lilja et al. 2008; Montastruc et al. 2015; Tampi et al. 2015). There are relatively few cases of this ADR published in the literature (Aström-Lilja et al. 2008; Tampi et al. 2015). Some trends can be discussed after description of these 35 cases of QT prolongation. This serious ADR was observed mainly in older patients, most of them being women and after a variable delay of exposure (days to years). In around two out of three reports, citalopram or escitalopram was associated with other pro-arrhythmic drugs, mainly cardiotropic or psychotropic ones, suggesting the importance of drug interactions in this ADR. However, in around 1/3 of cases, QT prolongation was observed with citalopram or escitalopram alone. As previously reported for drug-induced QT prolongation (Yap and Camm 2003), other associated factors were a significant previous medical history (mainly cardiac disease) and/or hypokalemia. The fact that QT prolongation could appear several years after drug introduction is not surprising, it could suggest that, in some patients, other factors are involved, beside the drug: for example, a potential role for aging could be suggested. The work in the FPVDB is also interesting to discuss the doses used. For citalopram, all patients received 20 mg daily, which is the recommended dose in patients older than 60 years (FDA Drug Safety Communication n.d.-a; FDA Drug Safety Communication n.d.-b). For escitalopram, range of doses was between 5 and 20 mg daily, with three patients older than 70 years receiving more than the 10 mg recommended dose. Thus, analysis of the FPVDB underlines that QT prolongation does occur in most of the present reports at usually recommended doses, thus justifying careful use in at risk patients, as defined above.

The present study has several interesting strengths. First, since it was performed in a large database, we decided to carefully review all the ICSRs to exclude false data or errors. Thus, the included reports were true validated ones. This relatively uncommon validation for a pharmacoepidemiological study was performed in the two investigated PVDB, VigiBase® and the French one. Second, the case/non-case method used in the present study is known to be able to detect relatively rare signals for ADRs (Montastruc et al. 2011; Faillie et al. 2016). Since QT prolongation is a rare ADR, the method used in the present work (disproportionality analysis in a pharmacovigilance database) is interesting and validated: it allows detecting a signal but cannot be considered as a true risk evaluation study. The same difficulties would occur

if the purpose of the study would be to investigate other rare rhythmic ADRs, like torsades de pointes or ventricular arrhythmias. Third, the significant result obtained with the positive control, methadone, adds significance to our results from a methodological point of view. Another interesting point is that the VigiBase® study involves reports from all the parts of world, enabling us to conclude that the results do involve all medical practices and patients in the world.

In contrast, the present work has some mandatory limitations inherent to the use of pharmacovigilance data. The first was underreporting although it is known that it does not change the results and significance of case/non-case study (Montastruc et al. 2011; Faillie et al. 2016). Another limitation could be the fact that some information (doses, associated drugs, previous medical history…) may be missing in some reports. In fact, the mean value of the completeness score in VigiBase® was quite satisfying (0.5). Exact QT (or QTc) values could be one of the missing data in the two databases. However, it is important to underline that all reports registered as QT prolongation were included in the present study, whether the QT value was indicated or not in the report, as usual in such pharmacovigilance studies. Such QT prolongation was previously validated when the report was registered in the PVDB. However, due to the data registered, we are unable to discuss the present reports in terms of QTc values. Thus, in order to avoid these inherent limitations, we also worked in the FPVDB where all the registered data are also medically validated (Vial 2016). The descriptive part of the study allows us to discuss some important associated factors. Unfortunately, we were unable, as usual in pharmacovigilance studies, to investigate the metabolizer status of the patients in order to explain some reports.

In conclusion, the present study, performed in real conditions of life, shows a clear signal of QT prolongation with only two SRIs, citalopram and escitalopram, but not with the four others, fluoxetine, fluvoxamine, sertraline or paroxetine. Vulnerable patients are aged subjects with a previous cardiac history and receiving one or more cardiovascular (or psychotropic) drugs. Two final proposals can be made. First, from a pharmacological point of view, one can conclude that SRI-induced QT prolongation is not a class effect. In fact, the mechanism of citalopram (and escitalopram) increase in QT value remains discussed. A direct blockade of the rapid potassium delayed rectifier current, encoded by the human ether-related gene, was proposed (Yap and Camm 2003). Second, from a practical point of view, the present study suggests that a careful risk benefit discussion should be performed in patients with a previous history of cardiac disorders (and especially cardiac arrhythmia) requiring citalopram (or escitalopram). In these at risk patients, a periodic cardiac monitoring with clinical evaluation and EKGs should be monitored. Another therapeutic choice could be another SRI.

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Contributors Ana Ojero-Senard, Justine Benevent, Mélanie Araujo, François Montastruc, and Jean-Louis Montastruc designed the study and analyzed the data. Leila Chebane and Melanie Araujo extracted the data, performed the analysis, and prepared the results. Ana Ojero-Senard and Jean-Louis Montastruc wrote the manuscript. All the other authors corrected and approved the manuscript.

Compliance with ethical standards

Conflict of interest None.

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