Letters

RESEARCH LETTER

Proton Pump Inhibitors Associated With Drug-Induced Lupus Erythematosus

The role of proton pump inhibitors (PPIs) in the occurrence of drug-induced lupus erythematosus (DILE) has been suggested for both drug-induced systemic lupus erythematosus (DI-SLE) and drug-induced cutaneous lupus erythematosus (DI-CLE) but remains poorly characterized.[1-3] Therefore, the aims of this study were, first, to investigate the pharmacovigilance signal of PPI-associated DILE using different indicator tools for disproportionate reporting and, second, to better characterize the spectrum of PPI-associated DILE by focusing on the type of DILE as well as therapeutic management.

Supplemental content

Methods | In this case series, we performed a disproportionality study using data from VigiBase, the World Health Organization's global pharmacovigilance database. This study was approved by all French Regional Pharmacovigilance Centers. Because this study used exclusively secondary and publicly available data, no ethical approval was required. For all PPIs and each molecule, a case-noncase study was performed to assess a potential pharmacovigilance signal in computing the information components (ICs) and reporting odds ratios (RORs). We also performed sensitivity analyses, taking into account only cases reported after January 1, 2002, and only those cases reported by physicians. In addition, we described clinical, immunological, and therapeutic management of the suspected PPI-associated DILE from the French pharmacovigilance database (eMethods in the Supplement). The level of significance assessed was $P < .05$. Statistical analyses were performed in RStudio, version 1.2.5001 (RStudio). Data were analyzed from December 2019 to September 2021.

Results | Among 21 104 559 cases reported in VigiBase from January 1985 to December 2019, 625 were DILE associated with a PPI. The median (IQR) age at onset of DILE was 59.0 (48.0-68.0) years, and 489 cases (78.2%) involved female patients. In 307 cases (49.1%), a PPI was the only suspected drug. Omeprazole was the most frequently involved PPI (n = 190; 30.4%). Statistical pharmacovigilance signals were observed for esomeprazole (IC_{025}, 0.67; ROR, 1.84; 95% CI, 1.60-2.13), lansoprazole (IC_{025}, 0.72; ROR, 1.97; 95% CI, 1.65-2.36), and omeprazole (IC_{025}, 0.70; ROR, 1.87; 95% CI, 1.63-2.13), concordant in sensitivity analyses (**Table 1**, see footnote "a" for complete definition of IC_{025}).

Among 791 922 cases reported in the French pharmacovigilance database between January 1985 and December 2019, 60 were DILE associated with a PPI. After reviewing 60 records, 49 patients were included (**Table 2**). The median (IQR) age was 68.0 (58.8-78.0) years, and 32 of 49 (65.3%) were female patients. Esomeprazole was the most frequently involved PPI (n = 23; 46.9%). An isolated DI-CLE was observed in 39 patients (79.6%), including subacute DI-CLE (n = 19; 48.7%), discoid DI-CLE (n = 2; 5.1%), tumidus DI-CLE (n = 1; 2.6%), and unspecified DI-CLE (n = 17; 43.6%). Seven patients (14.3%) had DI-SLE with cutaneous involvement, and most specified cases were of the subacute type (n = 3; 42.9%). The PPI was stopped in 35 of 41 patients (71.5%), in whom remission occurred in 18 of 35 patients (51.4%) without specific treatment.

Table 1. Reporting Odds Ratios (RORs) With Their 95% CIs and IC_{025}[a] for Drug-Induced Lupus Erythematosus With All Proton Pump Inhibitors (PPIs) and With Each Molecule Using VigiBase[b]

Metric	All PPIs	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
IC_{025}	0.65[c]	0.67[c]	0.72[c]	0.70[c]	−0.33	−2.86
ROR (95% CI)	1.72 (1.59-1.87)[c]	1.84 (1.60-2.13)[c]	1.97 (1.65-2.36)[c]	1.87 (1.63-2.13)[c]	1.17 (0.94-1.45)	0.95 (0.59-1.53)
Localization of reports, France						
IC_{025}	1.65[c]	1.78[c]	1.20[c]	0.94[c]	0.64[c]	2.61[c]
ROR (95% CI)	3.88 (2.98-5.05[c]	4.52 (3.01-6.80)[c]	4.22 (2.10-8.47)[c]	2.62 (1.54-4.45)[c]	3.37 (1.80-6.29)[c]	12.31 (6.11-24.80)[c]
Date, cases reported after January 1, 2002						
IC_{025}	0.76[c]	0.75[c]	0.84[c]	0.87[c]	−0.19	−2.07
ROR (95% CI)	1.86 (1.71-2.02)[c]	1.94 (1.68-2.24)[c]	2.12 (1.76-2.55)[c]	2.89 (2.56-3.26)[c]	1.26 (1.00-1.58)[c]	1.06 (0.67-1.70)
Reporter qualification, physician						
IC_{025}	1.19[c]	1.67[c]	1.51[c]	0.75[c]	1.00[c]	−0.34
ROR (95% CI)	2.57 (2.22-2.97)[c]	3.75 (2.87-4.91)[c]	3.55 (2.56-4.93)[c]	2.13 (1.66-2.73)[c]	2.61 (1.90-3.59)[c]	2.04 (1.06-3.93)[c]

Abbreviation: IC, information component.

[a] IC_{025} is the lower end of a 95% credibility interval for the IC. An IC_{025} of greater than 0 emits a pharmacovigilance signal.

[b] The noncases were patients exposed to the drug of interest with other drug reactions besides drug-induced lupus erythematosus and patients exposed to other drugs with other drug reactions. In sensitivity analyses, cases were compared with noncases in France reported after January 1, 2002, and reported only by physicians.

[c] Values indicate a statistical signal detection through VigiBase disproportionality analyses.

Table 2. Demographic, Clinical, Immunological, and Histological Characteristics of the Study Population Using the French Pharmacovigilance Database

Characteristic	Patients, No. (%) (n = 49)
Age, median (IQR), y (n = 48)	68.0 (58.8-78.0)
Sex	
Female	32 (65.3)
Male	17 (34.7)
History of autoimmune diseases	8 (16.3)
PPI	
Esomeprazole	23 (46.9)
Lansoprazole	5 (10.2)
Omeprazole	8 (16.3)
Pantoprazole	9 (18.4)
Rabeprazole	4 (8.2)
Onset time, median (IQR), wk (n = 33)	12.0 (4.0-52.0)
Drug imputability	
PPI only suspected drug	16 (32.6)
Several suspected drugs, of which PPI is the most suspected drug	19 (38.8)
Several suspected drugs, of which PPI has equivalent imputability	14 (28.6)
Cutaneous lupus erythematosus	39 (79.6)
Subacute	19 (48.7)
Discoid	2 (5.1)
Tumidus	1 (2.6)
NA	17 (43.6)
Systemic lupus erythematosus with cutaneous involvement	7 (14.3)
Subacute	3 (42.9)
Discoid	0
Tumidus	0
NA	4 (57.1)
Systemic lupus erythematosus without cutaneous involvement	3 (6.1)
Type of antibodies	
Antinuclear antibody (n = 39)	36 (92.3)
Anti-dsDNA (n = 36)	8 (22.2)
Anti-Sm (n = 35)	2 (5.7)
Anti-Ro/SSA (n = 38)	28 (73.7)
Anti-La/SSB (n = 35)	7 (20.0)
Histological confirmation	
Yes	32 (65.3)
No	9 (18.4)
NA	8 (16.3)
Seriousness criteria[a]	41 (83.7)
Deaths	0
PPI withdrawn or continued	
PPI withdrawn	35 (71.5)
Recovery without specific treatment	18 (51.4)
Recovery with specific treatment	8 (22.9)
NA	9 (25.7)
PPI continuation	6 (12.2)
Recovery without specific treatment	0
Recovery with specific treatment	3 (50.0)
NA	3 (50.0)
NA	8 (16.3)
Prescribed treatment	
Topical corticosteroids (n = 21)	19 (90.5)
Hydroxychloroquine (n = 31)	25 (80.6)
Oral corticosteroids (n = 34)	11 (32.3)
Immunosuppressives (n = 30)	2 (6.7)[b]
Prescribed treatment by lupus subtype	
Cutaneous lupus erythematosus	39 (79.6)
Topical corticosteroids (n = 21)	18 (46.1)
Hydroxychloroquine (n = 31)	20 (51.3)
Oral corticosteroids (n = 34)	4 (10.3)
Immunosuppressives (n = 30)	2 (5.1)
Systemic lupus erythematosus with cutaneous involvement	7 (14.3)
Topical corticosteroids (n = 21)	0
Hydroxychloroquine (n = 31)	4 (57.1)
Oral corticosteroids (n = 34)	4 (57.1)
Immunosuppressives (n = 30)	0
Systemic lupus erythematosus without cutaneous involvement	3 (6.1)
Topical corticosteroids (n = 21)	0
Hydroxychloroquine (n = 31)	1 (33.3)
Oral corticosteroids (n = 34)	3 (100.0)
Immunosuppressives (n = 30)	0
Recovery time, median (IQR), mo[c] (n = 15)	1.0 (0.75-1.5)

Abbreviations: NA, not available; PPI, proton pump inhibitor.

[a] Seriousness criteria were defined as a life-threatening disease, a hospitalization, an occurrence of a disability, or other seriousness criteria according to the reporter qualification.

[b] The immunosuppressive drug prescribed was thalidomide. Drug dosages were not specified.

[c] Time initiates with the beginning of medical care.

Discussion | In this case series using 2 large pharmacovigilance databases, we highlighted that PPIs are associated with pharmacovigilance signals for the occurrence of DILE. An association between PPIs and the risk of DILE has been suggested in several studies using IC_{025}.[1,2,4,5] The present study confirmed this finding using not only IC_{025}, but also ROR with data from 2 different databases and with sensitivity analyses performed. Moreover, we reported the therapeutic management of 49 PPI-associated DILE cases, which, to our knowledge, has never been done. Furthermore, accurate data on DILE subtypes associated with PPIs were scarce. This descriptive case series highlights that, first, PPIs may be associated with not only isolated DI-CLE, but also DI-SLE with or without cutaneous involvement. Second, among DI-CLE cases, subacute CLE is the most common subtype in contrast with discoid CLE in the general population. Finally, we also identified 2 cases of discoid CLE and 1 case of tumidus lupus, which emphasizes that other CLE subtypes may be associated with PPIs. Among the limitations of this study is the heterogeneity of the data available in the reports of adverse events. Moreover, the diagnosis of SLE and CLE may be confused with many other diseases. Therefore, we included only cases fulfilling validated classification criteria, and we performed sensitivity analyses to reduce the

Weber effect, which is an epidemiologic phenomenon inducing an increased number of reported adverse reactions during the first 2 years of drug marketing, and to avoid selection bias induced by adverse events reported by nonphysicians.[6]

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