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## **Research letter**

### **Pump protons inhibitors induced lupus erythematosus: a disproportionality study using the French national pharmacovigilance and the WHO pharmacovigilance database**

Short title: Pump protons inhibitors and drug-induced lupus erythematosus

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**Abbreviations:**

ANSM : Agence Nationale de Sécurité du Médicament et des Produits de Santé

DILE: Drug-induced Lupus Erythematosus

DI-SLE: Drug-induced Systemic Lupus Erythematosus

DI-CLE: Drug-induced Cutaneous Lupus Erythematosus

FPDB: French Pharmacovigilance Database

IC: Information Component

MedDRA: Medical Dictionary of Drug Regulatory Activities

NA: Not Available

OR: Odds Ratios

PPI: Pump Protons Inhibitors

ROR: Reporting Odds Ratios

Subacute DI-CLE: Drug-induced Subacute Cutaneous Lupus Erythematosus

VigiBase: WHO Pharmacovigilance Database

**Keywords:** cutaneous lupus erythematosus, systemic lupus erythematosus, side effects, proton pump inhibitors, pharmacovigilance, information component

**Dear Editor,**

The role of Protons 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 our study were 1) to investigate the pharmacovigilance signal of PPIs-induced DILE using different indicator tools for disproportionate reporting through the analysis of reported cases of the WHO pharmacovigilance database (VigiBase), 2) to better characterize the spectrum of PPIs-induced DILE focusing on the type of DILE (DI-SLE, DI-CLE and CLE subtypes), clinical and immunological features as well as therapeutic management of PPIs-induced DILE recorded in the French pharmacovigilance database (FPDB). We performed a disproportionality study using data from Vigibase, the global pharmacovigilance database. For all PPIs and for each molecule, a case-non case study was performed to assess a potential pharmacovigilance signal in computing information component (IC) and Reporting Odds Ratios (ROR). We also performed sensitive analyses, (i) taking into account only cases reported after January 1, 2002 and (ii) taking into account cases only reported by physicians. In addition, we described clinical, immunological and therapeutic management of the suspected PPIs-induced DILE from the FPDB.

Among 21,104,559 adverse drug reactions reported in VigiBase from January 1, 1985 to December 9, 2019, 23,778 were encoded as DILE and 625 were DILE induced by a PPI. A total of 221 (35.4%) DILE were induced by omeprazole, 190 (30.4%) by esomeprazole, 120 (19.2%) by lansoprazole, 77 (12.3%) by pantoprazole and 17 (2.7%) by rabeprazole. The median age of onset of DILE was 59.0 years old (IQR<sub>25-75</sub> 48.0-68.0), 78.2% (n=489) were women and in 49.1% (n=307) of cases, the PPI was the only suspected drug. Significant statistical pharmacovigilance signals were observed for esomeprazole (IC<sub>025</sub> 0.67 and ROR 1.84, 95%CI

1.60-2.13), for lansoprazole (IC<sub>025</sub> 0.72 and ROR 1.97, 95%CI 1.65-2.36) and for omeprazole (IC<sub>025</sub> 0.70 and ROR 1.87, 95%CI 1.63-2.13), concordant in sensitive analyses (**Table 1**).

Among 791,922 cases reported in the FPDB between January,1 1985 and December,9 2019, 775 were labeled as DILE and 60 were associated with a PPI. After reviewing the 60 side effect notifications, 9 cases were excluded due to the lack of immunological or histological confirmation and 2 cases were excluded because the imputability score of PPI was inferior to that of another drug. A total of 49 patients was included (**Table 2**). The median age was 68.0 years old (IQR<sub>25-75</sub> 58.75-78.0) and 32 patients (65.3%) were female. Esomeprazole was the most frequently involved PPI (n=23, 46.9%) followed by pantoprazole (n=9, 18.4%), omeprazole (n=8, 16.3%), lansoprazole (n=5, 10.2%) and rabeprazole (n=4, 8.2%). A total of 39 patients (79.6%) had an isolated DI-CLE, of which the main subtype was subacute DI-CLE (n=19, 48.7%), unspecified (n=17, 43.6%), discoid (n=2, 5.1%), tumidus (n=1, 2.6%). Seven patients had DI-SLE with cutaneous involvement (n=7, 14.3%) mostly subacute DI-CLE (n=3, 42.9%). Considering therapeutic management, data was available in 41 cases (83.7%). The PPI was stopped in 35/41 patients (71.5%), of which remission occurred in 18/35 (51.4%) without specific treatment.

Using two large pharmacovigilance databases, we highlighted that PPIs are associated with a significant pharmacovigilance signal for the occurrence of DILE. An association between PPI and the risk of DILE has been suggested in several studies (1,2,4,5), our study confirmed these finding using two tools frequently used to detect pharmacovigilance signals, IC<sub>025</sub> but also ROR, and using also two different databases. Moreover, we performed sensitive analysis in order to reduce bias in disproportionality studies (6). Early recognition of PPIs-induced DILE is crucial because withdrawal of the treatment is associated with rapid recovery in most cases.

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## Disclosure statement:

No author has a conflict of interest regarding this manuscript.

These reports originate from different sources such as healthcare professionals, patients, and pharmaceutical companies. The data used in this study come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the World Health Organization.

Pauline Bataille designed the work, acquired data and drafted the manuscript. Benedicte Lebrun Vignes designed the work and acquired data. Patricia Senet, Angele Soria and Florence Tubach contributed in revising critically the manuscript for important intellectual content. Francois Chasset and Annick Barbaud designed the work and drafted the manuscript.

Table 1: Reporting Odds Ratios (ROR) with their 95% confidence intervals and IC025 for all pump protons inhibitors and for each molecule using VigiBase

	<b>PPIs</b>	<b>esomeprazole</b>	<b>lansoprazole</b>	<b>omeprazole</b>	<b>pantoprazole</b>	<b>rabeprazole</b>
<b>IC<sub>025</sub></b>	<b>0.65</b>	<b>0.67</b>	<b>0.72</b>	<b>0.70</b>	-0.33	-2.86
<b>ROR, 95%CI</b>	<b>1.72</b> <b>(1.59-1.87)</b>	<b>1.84</b> <b>(1.60-2.13)</b>	<b>1.97</b> <b>(1.65-2.36)</b>	<b>1.87</b> <b>(1.63-2.13)</b>	1.17 (0.94-1.45)	0.95 (0.59-1.53)
<b>Localization of the reports</b>						
<b>France</b>						
IC <sub>025</sub>	<b>1.65</b>	<b>1.78</b>	<b>1.20</b>	<b>0.94</b>	<b>0.64</b>	<b>2.61</b>
ROR (95% CI)	<b>3.88</b> <b>(2.98-5.05)</b>	<b>4.52</b> <b>(3.01-6.80)</b>	<b>4.22</b> <b>(2.10-8.47)</b>	<b>2.62</b> <b>(1.54-4.45)</b>	<b>3.37</b> <b>(1.80-6.29)</b>	<b>12.31</b> <b>(6.11-24.80)</b>
<b>Date</b>						
<b>Cases reported after January 1, 2002</b>						
IC <sub>025</sub>	<b>0.76</b>	<b>0.75</b>	<b>0.84</b>	<b>0.87</b>	-0.19	-2.07
ROR (95% CI)	<b>1.86</b> <b>(1.71-2.02)</b>	<b>1.94</b> <b>(1.68-2.24)</b>	<b>2.12</b> <b>(1.76-2.55)</b>	<b>2.89</b> <b>(2.56-3.26)</b>	<b>1.26</b> <b>(1.00-1.58)</b>	1.06 (0.67-1.70)
<b>Reporter qualification</b>						
<b>Physicians</b>						
IC <sub>025</sub>	<b>1.19</b>	<b>1.67</b>	<b>1.51</b>	<b>0.75</b>	<b>1.00</b>	-0.34
ROR (95% CI)	<b>2.57</b> <b>(2.22-2.97)</b>	<b>3.75</b> <b>(2.87-4.91)</b>	<b>3.55</b> <b>(2.56-4.93)</b>	<b>2.13</b> <b>(1.66-2.73)</b>	<b>2.61</b> <b>(1.90-3.59)</b>	<b>2.04</b> <b>(1.06-3.93)</b>

PPIs: Pump Protons Inhibitors; IC: information component; CI : confidentiel interval

\* Values highlighted in bold indicate a statistical signal detection through VigiBase disproportionality analyses.

\*\* IC<sub>025</sub> is the lower end of a 95% credibility interval for the IC. IC<sub>025</sub>> 0 emits a pharmacovigilance signal.

Table 2: Demographic, clinical, immunological and histological characteristics of the study population using the French pharmacovigilance database

CHARACTERISTICS	Patients N= 49
<b>MEDIAN AGE (IN YEARS) MEDIAN (IQR<sub>25-75</sub>) (/48)</b>	68.0 (58.75-78.0)
<b>SEX (%)</b> Women	32 (65.3)
<b>HISTORY OF AUTOIMMUNE DISEASES (%)</b>	8 (16.3)
<b>PPI (%)</b> Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabéprazole	23 (46.9) 5 (10.2) 8 (16.3) 9 (18.4) 4 (8.2)
<b>MEDIAN ONSET TIME (IN WEEKS) (IQR<sub>25-75</sub>) (/33)</b>	12.0 (4.0-52.0)
<b>DRUG IMPUTABILITY (%)</b> PPI only suspected drug Several suspect drugs of which PPI is the most suspected drug Several drugs of which PPI has equivalent imputability than other drugs	16 (32.6) 19 (38.8) 14 (28.6)
<b>CUTANEOUS LUPUS ERYTHEMATOSUS (%)</b> Subacute Discoid Tumidus NA	<b>39 (79.6)</b> 19 (48.7) 2 (5.1) 1 (2.6) 17 (43.6)
<b>SYSTEMIC LUPUS ERYTHEMATOSUS WITH CUTANEOUS INVOLVMENT (%)</b> Subacute Discoid Tumidus NA	<b>7 (14.3)</b> 3 (42.9) 0 0 4 (57.1)
<b>SYSTEMIC LUPUS ERYTHEMATOSUS WITHOUT CUTANEOUS INVOLVMENT (%)</b>	<b>3 (6.1)</b>
<b>TYPE OF ANTIBODIES (%)</b> Antinuclear antibody (/39) Anti-DNA (/36) Anti-Sm (/35) Anti-Ro/SSA (/38) Anti-La/SSB (/35)	36 (92.3) 8 (22.2) 2 (5.7) 28 (73.7) 7 (20.0)
<b>HISTOLOGICAL CONFIRMATION (%)</b> Yes No NS	32 (65.3) 9 (18.4) 8 (16.3)
<b>SERIOUSNESS CRITERIA (%) *</b> Deaths	41 (83.7) 0
<b>PPI WITHDRAWN (%)</b> Recovery without specific treatment Recovery with specific treatment NS	<b>35 (71.5)</b> 18 (51.4) 8 (22.9) 9 (25.7)
<b>PPI CONTINUATION (%)</b> Recovery without specific treatment Recovery with specific treatment NS	<b>6 (12.2)</b> 0 3 (50.0) 3 (50.0)
<b>NA (%)</b>	<b>8 (16.3)</b>
<b>PRESCRIBED TREATMENT (%)</b> Topical corticosteroids (/21) Hydroxychloroquine (/31) Oral corticosteroids (/34) Immunosuppressives (/30)	19 (90.5) 25 (80.6) 11 (32.3) 2 (6.7) **
<b>MEDIAN RECOVERY TIME (IN MONTHS) (IQR<sub>25-75</sub>) *** (/15)</b>	1.0 (0.75-1.5)

IQR: Interquartile range; PPIs: Pump Protons Inhibitors; NA: not available.

\* Seriousness criteria was defined as a life-threatening disease, a hospitalization, an occurrence of a disability or another seriousness criteria according the reporter qualification.

\*\* The 2 immunosuppressives prescribed drugs were thalidomide. Drugs dosages were not specified.

\*\*\* Since the beginning of the medical care.