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Alimentary Tract

Spontaneous reporting of adverse reactions related to proton pump inhibitors

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely prescribed in all age groups, and their use is increasing. However, their safety profile has been frequently questioned.
Aims: The aim of this study was to analyze the characteristics of PPI-related adverse drug reactions (ADRs) reported to the Italian spontaneous reporting system (SRS) database and relative to an Italian region (Sicily).
Methods: A 20-year observational, retrospective study was conducted, evaluating PPI-related ADR reports from Sicily between January 1st, 2001, and June 30th, 2021. The factors associated with ADR seriousness were investigated.
Results: A total of 148 spontaneous reports of ADRs related to PPIs were analyzed. Lansoprazole was the drug with the highest number of associated reports (30.87%). The most frequently reported ADRs were cutaneous (24.56%) and/or gastrointestinal manifestations (18.10%), the latter especially in the case of lansoprazole-related ADRs ($p<0.006$). The great majority of ADR reports were relative to on-label prescriptions. Serious ADRs were 39 (26.35%). Serious ADRs were more common in reports including omeprazole than in reports containing other PPIs ($p<0.008$) and in reports presenting PPIs combined with other drugs than in reports with PPI single therapies ($p<0.001$).
Conclusion: Most PPI-related ADRs are non-serious. Omeprazole and combination therapy seem to be associated with ADR seriousness.

1. Introduction

The use of proton pump inhibitors (PPIs) has steadily increased during the last few decades. According to data from the Organization for Economic Cooperation and Development [1], the use of antiulcer agents in many European countries has nearly quadrupled since 2000, owing primarily to an increase in the use of PPIs. Consistently, evidence of adverse drug reactions (ADRs) associated with PPIs is growing and gaining the attention of authorities and healthcare professionals [2–4]. Through a variety of mechanisms, PPIs can have potentially deleterious effects, including endothelial dysfunction, hypomagnesemia, drug-drug interactions, decreased absorption of certain nutrients, bacterial overgrowth of the small intestine, decreased immune response, tubular interstitial inflammation, and increased bone turnover [5]. PPI-related ADRs can vary and generally include enteric infections, pneumonia, bone fractures, nutritional deficiencies, acute interstitial nephritis, and an increased risk of drug interactions [6].

Although several studies have investigated the ADRs of PPIs, real-life data regarding the safety profile of these molecules are limited, especially in Italy. Despite its inherent limitations, spontaneous reporting is fundamental to signal and alert generation in drug safety. The aim of this study was to analyze the characteristics (symptoms, time of onset, seriousness, risk factors) of ADRs in PPI therapy reported in the Italian Spontaneous Reporting System (SRS) database and relative to the Sicilian region.

2. Materials and methods

2.1. Study design

A 20-year observational, retrospective study was conducted, evaluating PPI-related ADRs reported in the Italian Spontaneous

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Reporting System (SRS) database and relative to the Sicilian region between January 1st, 2001, and June 30th, 2021. The Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) approved the use of the Italian SRS database (*Rete Nazionale di Farmacovigilanza*, RNF). No personal identifiers were collected from patients. The Ethics Committee of the G. Martino University Hospital approved this study (date 06/29/2020, n. 44/20).

2.2. Data collection

The RNF database was established in January 2001 and is maintained by AIFA with the aim of collecting all spontaneous reports of suspected ADRs received by patients or citizens, as well as healthcare professionals. As of June 2021, this database includes 644 361 reports of suspected ADRs, 32 518 of which were related to Sicily. Medicinal products were categorized by the Anatomical Therapeutic Chemical (ATC) classification (ATC code A02BC - formulations containing one or more PPIs in combination), and suspected ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®, version 23.0), with an emphasis on the System Organ Class (SOC) and Preferred Term (PT) levels. Suspected ADRs were considered serious if they were: (i) life-threatening or determined the patient's death, (ii) requiring or prolonging hospitalization, (iii) causing persistent or significant disability, (iv) representing a congenital anomaly/birth defect, or v) the presence of other medically important conditions, as determined by medical judgment or the European Medicines Agency's Important Medical Event (IME) list (version 23.0) [EMA website: Home/Human regulatory/Post-authorization/Pharmacovigilance/EudraVigilance/System overview].

2.3. Data analysis

A descriptive analysis was used to examine the sociodemographic characteristics of the study population as well as the characteristics of the recorded ADRs. Means and standard deviation (SD) were calculated for the anthropometric values. The ADR reports were grouped based on age, gender, number of suspected drugs in the report, duration of therapy, and the appropriateness of the PPI prescription. The adherence to approved use cases was evaluated for each ADR case by comparing the reported information to the Summaries of Product Characteristics available in the EMA database [7]. Differences in the seriousness of the ADRs assessed using the chi-square test were considered significant if the associated p-value was 0.05. The difference in days between the start of treatment and the onset of suspected ADRs was calculated to measure the time to onset (TTO) of ADRs. Reports with missing data regarding the date of initiation of therapy or the date of occurrence of adverse events were excluded from the TTO analysis. The predictive value of PPI dose, duration of therapy, and TTO on ADR seriousness was assessed using a univariate logistic regression model for each possible predictive variable. The data processing software R: A Language and Environment for Statistical Computing, Basic Package Version 3.6.3 was used for statistical analysis.

3. Results

They were reported 148 ADRs related to PPI administration, accounting for 0.02% of all reports (n = 548 260) and 4.41% of all PPI-related ADR reports (n = 3 355) in the RNF. A mean value of 7.4 ADR reports per year was observed, with a peak in 2007 (n = 24) (Fig. 1), likely due to an overall increased use of PPI in those years, influenced by the activation of several active pharmacovigilance projects in Italy. Considering the geographical distribution of the reports, most (n = 78) were from eastern Sicily, while 58 were from western Sicily. The others were obtained either through the Sicilian Regional Pharmacovigilance Center (n = 3) or AIFA itself (n = 9).

In most cases (n = 118; 79.72%), ADRs were reported by physicians, followed by pharmacists (n = 15; 10.13%), other healthcare professionals (n = 11; 7.43%), and patients in four cases (2.7%). In terms of patient characteristics, the male to female ratio was 1:1, and the mean observed age was 55.6 years, with a SD of 1.5 years. Patients' age ranged from 4 to 87 years; in detail, 32.43% of reports (n = 48) included patients aged 40–59 years, 28.37% of reports (n = 42) patients aged 60–75 years, 20.27% of cases (n = 30) patients aged 19–39 years, and 16.89% of cases (n = 25) patients aged 75 years or older. There were only two (1.35%) pediatric patients (0–18 years). In 32 cases, PPI was not the sole suspected drug, including the case in which the suspected PPIs were two (omeprazole and pantoprazole). Other suspected concomitant therapies included antibacterials for systemic use (ATC J01, n = 12), anti-inflammatory and antirheumatic products (ATC M01, n = 7), and antithrombotic agents (ATC B01, n = 7). Considering the distribution of reports in terms of suspected PPI, in a non-mutually exclusive fashion (in order to account for the case in which there were two PPIs reported as suspected), lansoprazole was reported in the majority of cases (n = 46, 30.87%), followed by pantoprazole (n = 31, 20.80%), esomeprazole (n = 30, 20.13%), omeprazole (n = 25, 16.77%), and rabeprazole (n = 17, 11.40%). Sufficient information to evaluate the adherence of the described therapy to approved use cases was available in 111 (75%) ADR cases. The characteristics of the therapeutic regimens with PPIs are represented in Table 1.

The median TTO was 4 [IQR: 0–20] days. Most ADRs presented 15 days after the start of PPI treatment (n = 38, 25.7%), with the remainder occurring within the first 24 h (n = 35, 23.6%), first 3 days (n = 31, 20.9%), or first 15 days (n = 32, 21.6%) of treatment. Skin and subcutaneous tissue seemed to be the most affected systems by ADRs, followed by the gastrointestinal tract. Pruritus (n = 15), rash (n = 12), erythema (n = 11), and urticaria (n = 9) were the most reported skin manifestations. Diarrhea (n = 17) and abdominal pain (n = 14) were the most common gastrointestinal complaints. Headaches were also quite frequent, with 13 cases documented. Table 2 reports the classification of ADRs by system organ class (SOC) and based on the various molecules. Significant differences in reporting rates among ADRs stratified by suspected drugs were observed for ADRs defined as gastrointestinal manifestations (p = 0.041). Post-hoc analyses were performed to validate these findings, highlighting that the occurrence of gastrointestinal disorders as ADRs was significantly associated (more frequently reported) with lansoprazole and less frequently reported with pantoprazole ($p < 0.006$ and $p < 0.034$, respectively). See Supplementary Table 1 for details on the observed ADRs at the MedDRA® Preferred Term level for each SOC.

Data regarding the seriousness of the described ADRs were available in 128 (86.5%) reports. Overall, the majority of PPI-related ADRs (n = 89, 60.13%) were non-serious. There were 39 (26.35%) serious ADRs, while the seriousness of the ADR could not be determined in 20 cases. Among the serious ADRs, 24 (16.21%) required hospitalization, 9 (6.08%) resulted in a medically important condition, 5 (3.37%) were life-threatening, and 1 (0.67%) caused severe or irreversible invalidity. Regarding the observed outcomes, 54.72% of cases (n = 81) showed complete resolution of the ADR, 18.91% (n = 28) reported an improvement in the reaction, in 6.75% of cases (n = 10) the patient had not yet recovered, and in one case the resolution of the ADR was accompanied by sequelae. An additional 28 cases (18.91%) did not have the ADR outcome recorded.

Tables 3 and 4 show the variables associated with serious and non-serious ADRs. The percentage of serious reports was significantly higher in the group of ADRs caused by omeprazole compared to other PPIs ($p < 0.008$), as well as in the group presenting

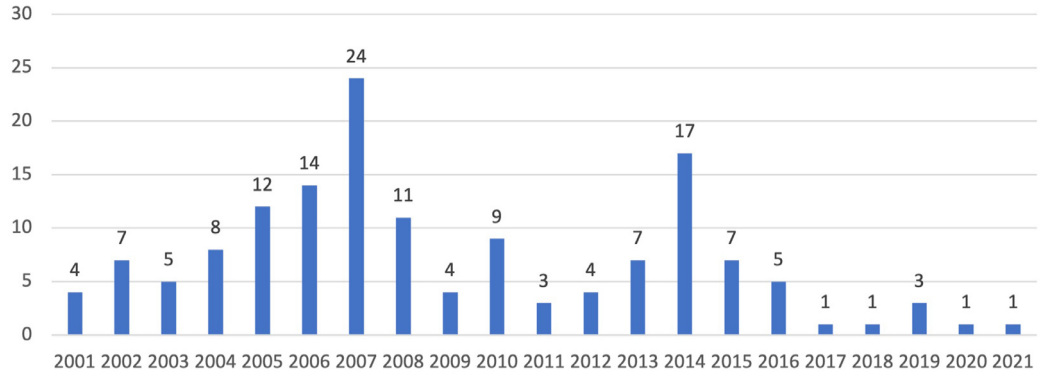

Fig. 1. The distribution of reports of proton pump inhibitor-related adverse drug reactions per year (2001–2021).

Table 1
Characteristics of PPI treatments.

Variable	Total n = 148 (%)
Duration of treatment, months n (%)	
≤2	102 (68.91)
3–12	8 (5.40)
>12	14 (9.45)
Not reported	24 (16.21)
Duration of treatment, days (median, SD)	8.89 ± 2.59
Multiple suspected drugs, n (%)	
No	116 (78.37)
Yes[a,b]	32 (21.62)
PPI and antibacterials for systemic use, n	12
PPI and anti-inflammatory and antirheumatic products, n	7
PPI and antithrombotic agents, n	7
PPI and agents acting on the renin-angiotensin system, n	6
PPI and drugs for obstructive airway disease, n	4
PPI and antianemic preparations, n	3
Label, n (%)	
On	110 (74.32)
Off	1 (0.67)
Not available	37 (25)
Indication, n (%)	
GERD	28 (18.91)
Esophagitis	17 (11.48)
Gastritis	13 (8.78)
Prophylaxis (i.e., during treatment with NSAIDs, or for stress ulcer bleeding in ICU)	11 (7.43)
Epigastric pain	6 (4.05)
Duodenal ulcer	6 (4.05)
Hiatal hernia	5 (3.37)
Gastric ulcer	5 (3.37)
Esophageal disease (not specified)	4 (2.7)
Helicobacter pylori infection	2 (1.35)
Dyspepsia	1 (0.67)
Barrett's esophagitis	1 (0.67)
Esophageal varices	1 (0.67)
Acute pancreatitis	1 (0.67)
Gastrointestinal disorder (not specified)	1 (0.67)
Not reported	37 (25)

PPI, proton pump inhibitor.
SD, standard deviation.
GERD, gastroesophageal reflux disease.
NSAIDs, nonsteroidal anti-inflammatory drugs.
ICU, intensive care unit.
[a] The ADR cases distribution by other suspected drugs is not mutually exclusive.
[b] Drug classes found in fewer than three cases were excluded from this table.

multiple suspected drugs compared to those presenting only one suspected drug ($p < 0.001$). There was no statistically significant difference in TTO between serious and non-serious ADRs (during the first 24 h, 3 or 15 days of treatment, or 15 days after the start of treatment) ($p = 0.408$). Moreover, no association was found between the specific type of seriousness of these 39 serious ADRs (hospitalization, life-threatening, invalidity, or other medically important conditions) and their labels ($p = 0.981$). Furthermore, no significant predictive value on ADR seriousness was observed in relation to PPI dose [odds ratio (OR) = 1,02; (95% CI = 0,98 - 1,05)], treatment duration [OR = 1,00; (95% CI = 1,00 - 1,00)] and TTO [OR = 1,00; (95% CI = 1,00 - 1,00)].

4. Discussion

PPIs are one of the most commonly prescribed drugs in the United States and Europe [2,8], despite their association with a variety of ADRs, particularly after long-term use. The present study

Table 2
Distribution of reports of ADRs (n) by SOC according to MedDRA®.

SOC	Lansoprazole $n = 46$ (%)	Pantoprazole $n = 31$ (%)	Esomeprazole $n = 30$ (%)	Omeprazole $n = 25$ (%)	Rabeprazole $n = 17$ (%)	Total $n = 233$ (%)[a]	p[b]
Skin and subcutaneous tissue disorders	17 (23,94)	18 (36,73)	10 (20,41)	8 (19,51)	5 (21,74)	58 (24,89)	0.171
Gastrointestinal disorders	20 (28,17)	4 (8,16)	9 (18,37)	5 (12,2)	4 (17,39)	42 (18,03)	0.041*
Nervous system disorders	5 (7,04)	4 (8,16)	8 (16,33)	3 (7,32)	2 (8,7)	22 (9,44)	0.368
General disorders and administration site conditions	7 (9,86)	4 (8,16)	5 (10,2)	2 (4,88)	3 (13,04)	21 (9,01)	0.879
Respiratory, thoracic, and mediastinal disorders	2 (2,82)	5 (10,2)	3 (6,12)	1 (2,44)	1 (4,35)	12 (5,15)	0.355
Eye disorders	3 (4,23)	2 (4,08)	4 (8,16)	1 (2,44)	2 (8,7)	12 (5,15)	0.689
Musculoskeletal and connective tissue disorders	1 (1,41)	–	3 (6,12)	3 (7,32)	2 (8,7)	9 (3,86)	0.160
Vascular disorders	1 (1,41)	3 (6,12)	1 (2,04)	3 (7,32)	1 (4,35)	9 (3,86)	0.402
Investigations	2 (2,82)	2 (4,08)	1 (2,04)	3 (7,32)	–	8 (3,43)	0.472
Psychiatric disorders	2 (2,82)	1 (2,04)	1 (2,04)	3 (7,32)	–	7 (3)	0.956
Immune system disorders	5 (7,04)	–	–	1 (2,44)	–	6 (2,58)	0.065
Reproductive system and breast disorders	1 (1,41)	2 (4,08)	1 (2,04)	1 (2,44)	1 (4,35)	6 (2,58)	0.899
Metabolism and nutrition disorders	2 (2,82)	1 (2,04)	1 (2,04)	1 (2,44)	–	5 (2,15)	0.943
Ear and labyrinth disorders	1 (1,41)	1 (2,04)	1 (2,04)	1 (2,44)	1 (4,35)	5 (2,15)	0.967
Cardiac disorders	2 (2,82)	1 (2,04)	–	–	1 (4,35)	4 (1,72)	0.608
Blood and lymphatic system disorders	–	–	–	2 (4,88)	–	2 (0,86)	–
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	–	–	–	1 (2,44)	–	1 (0,43)	–
Infections and infestations	–	–	–	1 (2,44)	–	1 (0,43)	–
Hepatobiliary disorders	–	–	–	1 (2,44)	–	1 (0,43)	–
Injury, poisoning, and procedural complications	–	–	1 (2,04)	–	–	1 (0,43)	–
Renal and urinary disorders	–	1 (2,04)	–	–	–	1 (0,43)	–

ADRs, adverse drug reactions.
SOC, system organ class.
[a] The total number includes the case in which there were two suspected PPIs.
[b] Differences for SOCs observed in fewer than three cases were not calculated.
* Statistically significant.

Table 3
Differences in demographic characteristics between serious and non-serious ADRs.

Variable		Non-serious ($n = 89$) [a] (n,%)	Serious ($n = 39$)[a] (n,%)	p
Gender	Male	49 (72.1)	19 (27.9)	0.508
	Female	40 (66.7)	20 (33.3)	
Age, years	0–18	1 (50)	1 (50)	0.887
	19–39	20 (74.1)	7 (25.9)	
	40–59	26 (65)	14 (35)	
	60–75	26 (72.2)	10 (27.8)	
	>75	15 (68.2)	7 (31.8)	

ADRs, adverse drug reactions.
[a] ≥ 1 missing data.

Table 4
Differences in PPI treatment characteristics between serious and non-serious ADRs.

Variable		Non-serious ($n = 89$)[a] (n,%)	Serious ($n = 39$)[a] (n,%)	p
Molecule[b]	Lansoprazole Pantoprazole	33 (80.5)	8 (19.5)	0.070
	Omeprazole	17 (63)	10 (37)	0.387
	Esomeprazole Rabeprazole	12 (48)	13 (52)	<0.008*
		17 (70.8)	7 (29.2)	0.899
		11 (91.7)	1 (8.3)	0.082
Multiple suspected drugs	Yes	13 (43.3)	17 (56.7)	<0.001*
	No	76 (77.6)	22 (22.5)	
Label	Off	1	0	0.518
	On	69 (70.4)	29 (29.6)	

PPI, proton pump inhibitor.
ADRs, adverse drug reactions.
[a] ≥ 1 missing data.
[b] ADR distribution by PPI non mutually exclusive.
* Statistically significant.

focused on PPI-induced ADRs in patients from Sicily. ADRs were spontaneously reported over a period of 20 years. Lansoprazole has been associated with the highest number of ADR reports, with cutaneous manifestations and/or gastrointestinal symptoms being the most frequently reported reactions. Skin manifestations (urticaria and urticaria/angioedema) were the most common side effects of PPIs in another Italian study of patients ($n = 12$) with a history of hypersensitive reactions to PPIs in an academic center between 2008 and 2013 [9]. A recent literature review analyzed 56 articles on PPI-induced cutaneous adverse reactions, including both immediate and delayed-type hypersensitivity reactions [12]. Although all PPIs can cause rapid immunoglobulin E-mediated reactions, previously reported cases of delayed-type hypersensitivity reactions included lansoprazole, esomeprazole, and omeprazole [11].

The mechanism of PPI-induced hypersensitivity reactions is not fully understood, but it is believed that the damaging agent in some PPIs is the sulfur moiety on the benzimidazole ring, which is modified in esomeprazole, omeprazole, and pantoprazole [12]. In any case, the present study found no association between skin manifestations and any of these molecules. Notably, ADRs classified as gastrointestinal disorders were reported more frequently with lansoprazole ($p < 0.006$). PPIs can produce dysbiosis as early as one week of usage. Dysbiosis has been linked to gastrointestinal diseases caused by chronic PPI use [10].

In prescription-event monitoring cohort studies, data on dispensed prescriptions prescribed by general practitioners in England shortly after each drug launch were linked to subsequent clinical events recorded by the prescriber [13]; 16,205 patients prescribed omeprazole, 17,329 patients prescribed lansoprazole, and 11,541 patients prescribed pantoprazole were studied. The most prevalent ADRs in the omeprazole, lansoprazole, and pantoprazole cohorts were diarrhea, nausea, vomiting, abdominal pain, and headache, with minimal absolute differences in the rate of most reactions between the three PPIs. However, diarrhea has been associated more frequently with lansoprazole than with omeprazole [13]. Treatment with lansoprazole 15 or 30 mg (depending on weight) once daily for 8–12 weeks led to gastrointestinal symptoms and headache as ADRs in two small ($n = 66$ [15] and $n = 87$ [14]) open-label, uncontrolled, multicenter trials in patients with gastro-esophageal reflux disease (GERD) aged 1–11 years and 12–17 years, respectively. Constipation occurred in 5% of the patients in the first study, while in the other study, abdominal pain was experienced by 5% of the patients, and nausea and dizziness by 3% of the patients each [15,14]. Only one patient in the second study reported skin manifestation in the form of a rash [15].

Similarly, AEs occurred in 62% of the 81 lansoprazole-treated subjects of 162 infants with persistent symptoms attributed to GERD who were randomly assigned to lansoprazole or placebo treatment for 4 weeks. AEs included diarrhea, constipation, vomiting, dermatitis, and eczema [16].

A minority of ADRs ($n = 39$) were found to be serious in this study. A significantly higher proportion of serious ADRs were observed in reports presenting as suspected drug omeprazole, as well as reports presenting as suspected drug PPIs and other medications such as antibiotics. Experience of the adverse effects of PPIs is greatest for omeprazole, which has been on the market the longest [5,13]. To the best of our knowledge, no previous studies have shown a clear association between omeprazole and the seriousness of the ADR in comparison to other PPIs. The overall frequency of reported serious ADRs was higher in the SOPRAN study [17] than in the LOTUS study [18] (two controlled, randomized clinical studies comparing antireflux surgery to long-term therapy with omeprazole and esomeprazole, respectively), but the median exposure time was two-fold longer in the SOPRAN study than in the LOTUS study, and the patients were older on average in the former study (median of 51–55 versus 45 years) [18,19]. In a survey on the prevalence of hospitalizations due to ADRs, omeprazole was the drug most associated with hospital admission [19]. Anyway, the safety of a drug may change over time due to increased use and patients' characteristics, so risk assessment is essential. A retrospective study of drug-drug interactions in elderly adults found 912 interactions, with 31.5% potentially contributing to ADRs [20]. The most frequent combinations were warfarin and heparin, warfarin and a statin, and warfarin and a PPI. At least one drug-drug interaction was responsible for 66 hemorrhages out of 122 (54%) and 41 elevated international normalized ratios (INRs) out of 54 (76%) [20]. Among the analyzed ADRs presenting more than one suspected drug in the present study, the presence of drug interactions already documented by literature sources was identified. Interactions of moderate entities between PPIs and acetylsalicylic acid-based preparations may affect salicylate oral bioavailability [21]. Concurrent use of PPIs and atorvastatin may result in a moderate pharmacokinetic interaction with an increase in atorvastatin plasma concentrations and an increased risk of myopathy [22]. However, a disproportionality analysis using the Italian national network of pharmacovigilance database found that the PPIs-statins combination was not associated with an enhanced reporting OR of muscular ADRs/rhabdomyolysis compared with statins alone [23]. Instead, it was shown to have a potential disproportionate reporting for the association between PPIs and rhabdomyolysis (reporting OR 1.667, 95% CI 1.173–2.369; $p < 0.01$) [23]. Finally, coadministration of PPIs with levothyroxine may decrease the latter's bioavailability. In this study, antibiotics were the most frequently reported drugs in combination with PPI. The most common and well-known indication for the use of PPIs in combination with antibiotics is the treatment of Helicobacter pylori infection. A retrospective study found links between the use of acid-suppressive medications (PPI, especially lansoprazole, or a histamine-2 receptor antagonist) and antibiotics in the first 6 months of life and the development of allergic diseases [24]. However, patients who are prescribed combined therapy, on the other hand, are more likely to have multiple medical conditions that may induce symptoms that could be misinterpreted as ADRs. In this study, the majority (74.32%) of PPI prescriptions were on-label, in contrast to the findings of many other previously published studies [4]. The steady increase in PPI use over the last few decades has been correlated to its overuse with potentially inappropriate indications such as inaccurate diagnosis of gastric-related conditions or gastroprotection in drug-related mucosal damage. In this study, neither the seriousness nor the outcome of serious ADRs were found to be related to the label.

The present study mainly focused on adults (>18 years of age), who accounted for the vast majority of patients for whom a PPI-related adverse reaction report was made (146/148, 98.65%). The recent pharmacovigilance study in children using the same database found 70 PPI-related adverse reaction reports in children in the Italian SRS database between 2001 and 2020, most of which (68.6%) were not serious or irreversible and presented with gastrointestinal (24%) and/or skin manifestations (21.3%) [25]. Notably, combination therapy (i.e., antibiotics) was positively associated with the severity of ADR in children as well [25].

This study has some limitations: (i) only a minority of ADR reports included information on the causative relationship between the drugs and the reported ADR; (ii) ADR incidence estimations could not be calculated because the database used for the analysis contained no information regarding the total number of patients treated with PPIs for the considered geographic area; (iii) the relationship between the rate of ADRs and the market share in the given region was not investigated because data on the sales volume for PPIs in Sicily for the considered timeframe were not available; (iv) several reporting biases could have influenced the results. When using SRS data, confounding by concomitant comorbidities cannot be excluded. Data from randomized controlled clinical trials and/or epidemiologic studies are required to clarify the associations obtained using SRS. Nonetheless, data mining using such unique resources can reveal useful information on potential ADRs.

5. Conclusions

This was a 20-year observational study based on spontaneous reports of PPI-related ADRs. The majority of PPI-related ADRs were neither serious nor irreversible, and omeprazole and combination therapy appeared to be associated with ADR seriousness. Patients who are prescribed combined therapy, on the other hand, are likely to have comorbidities that create clinical scenarios that could be misinterpreted as ADRs. In addition to the efficacy of PPIs, under-

standing ADRs is important when deciding whether to prescribe these medications. These findings could help to support claims for using PPI and other drugs only when there is a demonstrable clinical benefit. Studies highlighting the potential risks of such widely used medications should be implemented in order to provide real-world evidence to healthcare providers and assist them in making shared decisions when discussing PPI therapy with their patients.

Conflict of interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.10.024.

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