Acute pancreatitis following treatment with protease inhibitors, which may be potential therapeutics for COVID-19: A real-world analysis of postmarketing surveillance data

Lei Zhang (zergzl@163.com)
Department of Pharmacy, China Japan Friendship Hospital https://orcid.org/0000-0002-5832-7175
Bin Zhao
Peking Union Medical College Hospital
Yongguang Shang
China-Japan Friendship Hospital Department of pharmacy
Wangjun Qin
China Japan Friendship Hospital

Research article

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Abstract

Backgrounds: The potential therapeutic effects of protease inhibitors (PIs), such as lopinavir/ritonavir and darunavir, on COVID-19 are being tested in clinical trials. Although acute pancreatitis (AP) has been reported in patients treated with PIs, there have been few real-world studies comparing the occurrence and characteristics of AP after different PI regimens.

Methods: Disproportionality analysis and Bayesian analysis were utilized for data mining of the Food and Drug Administration's Adverse Event Reporting System (FAERS) database for suspected adverse events involving AP after PI from January 2004 to December 2019. The times to onset and fatality rates of AP following different PI regimens were also compared.

Results: Based on 33,832 reports related to PIs, 285 cases (0.84% of total adverse drug reactions, ADRs) were associated with AP; in these reports, the number of AP cases reported for the top five PIs was as follows: ritonavir/dasabuvir/ombitasvir/paritaprevir, 64 (22.46%); ritonavir, 54 (18.95%); atazanavir, 52 (18.25%); lopinavir/ritonavir, 48 (16.84%); and darunavir, 26 (9.12%). Twelve out of the 15 studied PIs, including lopinavir/ritonavir, darunavir and nelfinavir, which are potential therapeutics for COVID-19, were associated with AP. Of all the reported adverse events involving AP related to PIs, 64.56% occurred in men, which was a much higher proportion than what was observed in women (28.42%). The median time to onset of AP was 103 (IQR: 26-408) days after the initiation of PI treatment. Patients treated with ritonavir/dasabuvir/ombitasvir/paritaprevir appeared to have an earlier onset of AP than those receiving atazanavir (31 [IQR: 17–68.25] days vs 187.5 [IQR: 80.5–556.5] days, p=0.0379) or ritonavir (31 [IQR: 17–68.25] days vs 177 [IQR: 56–539] days, p=0.0371). Compared with AP cases induced by all studied PIs, which had a fatality rate of 14.02%, AP cases associated with ritonavir (18.87%) and lopinavir/ritonavir (22.73%) appeared to be associated with a higher risk of death.

Conclusions: Analysis of the FAERS data provides a more precise understanding of the occurrence and characteristics of AP after different PI regimens. Signals for AP associated with various PI regimens have been detected. The findings support continued surveillance, risk factor identification, and comparative studies.

Declarations

Ethics approval and consent to participate As this was an observational and retrospective study, and the database is open to the public, this study was exempt from approval by China Japan Friendship Hospital Institutional Review Board.

Consent for publication Not applicable

Availability of data and material All adverse event reports extracted during the current study are available in the FDA's Adverse Event Reporting System (FAERS) database [https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html]. And all data generated and analyzed during the study has been presented in the tables and figures. Other related information is available under request to the corresponding author.

Competing interest The authors declare that they have no competing interests that are directly relevant to the content of this study.

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Authors' contributions Lei Zhang designed the research, analyzed and interpreted data, wrote the manuscript draft, and corrected it. Bin Zhao designed the research, participated in the interpretation of data, and corrected the manuscript. Yongguang Shang participated in the interpretation of data and writing of the manuscript draft. Wangjun Qin participated in the study design, plotted figures, and collected data.

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Introduction

As of May 24, 2020, coronavirus disease 2019 (COVID-19), which is caused by a novel coronavirus (named SARS-CoV-2 by WHO) and was first identified in Wuhan, China, has spread globally. The number of globally confirmed cases is more than 5204,000 as of the submission of this manuscript[1]. To date, there are no specific treatments for COVID-19. Identifying effective and safe drugs to treat the virus as soon as possible is critical for the response to the COVID-19 outbreak.

The combination of lopinavir and ritonavir is widely used as a pharmacologically boosted protease inhibitor (PI) in highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV)-infected patients [2, 3]. Due to its demonstrated efficacy in treating pneumonia associated with severe acute respiratory syndrome coronavirus (SARS-CoV)[4] and Middle East respiratory syndrome coronavirus (MERS-CoV)[5,6] in addition to its activity against SARS-CoV-2 in vitro, lopinavir/ritonavir has been applied to treat COVID-19, and some cases have been reported [7, 8]. Triple combination therapy with ritonavir/lopinavir, ribavirin and interferon-alpha has been recommended as a drug treatment option by the guidelines for the diagnosis and treatment of COVID-19 (trial version 7), which was published by the National Health Commission of China. Nelfinavir, another PI that can strongly inhibit the replication of SARS-CoV[9], may also be a candidate drug for COVID-19.

In the absence of a specific treatment for COVID-19, several subsequent clinical trials (ChiCTR2000030187, ChiCTR2000029741, ChiCTR2000029603, ChiCTR2000029573, ChiCTR2000029548, ChiCTR2000029541, ChiCTR2000029539, ChiCTR2000029468, ChiCTR2000029387, and ChiCTR2000029308) have been quickly conducted in China to test the efficacy and safety of lopinavir/ritonavir and darunavir/cobicistat (another boosted PI) as monotherapies or

combination therapies for the treatment of COVID-19-associated pneumonia in more than 10 hospitals[10]. Under this circumstance, not only the efficacy but also the safety of these PIs for the treatment of COVID-19 still need to be further confirmed.

As part of HAART, PIs have led to a significant decline in HIV-related morbidity and mortality[11]. However, PI-based treatments are, in general, associated with changes in the distribution of body fat and metabolic disorders, such as insulin resistance, hypercholesterolemia, and hypertriglyceridemia[12-15]. The latter is usually severe and difficult to control and may trigger episodes of AP[16]. PI-associated pancreatitis, some cases of which were fatal, has been observed[17, 18]. The risk of severe pancreatitis induced by PI therapy has attracted a great deal of attention. Previous studies have evaluated whether the etiology of AP has changed since PI-based HAART therapy was first introduced in 1996[19-22]. However, past studies have reported conflicting results regarding the impact of PIs on the development of pancreatitis[16]. Moreover, most evidence supporting the causal relationship between AP and PIs has come from case reports[23-25] and is insufficient to provide an overview of the risk of rare adverse events such as AP.

Pharmacovigilance studies regarding PI-induced AP events are still scarce. In particular, we still know little about the safety profile of PI regimens in regard to pancreatitis in clinical practice. Characterizing PI-associated pancreatitis may provide important clues for patient safety during antiviral therapy. By analyzing adverse events extracted from the FDA's Adverse Event Reporting System (FAERS) database, we focused on evaluating and comparing the associations between various PI regimens and AP in a large real-world patient population. In addition, we investigated fatality rates and the times to onset of AP after the administration of various PI regimens.

Materials And Methods

2.1 Data source

We conducted a retrospective pharmacovigilance study using the FAERS database data from January 2004 to December 2019. The FAERS is a public voluntary spontaneous reporting database that provides information on adverse event and medication error reports submitted by health professionals, consumers, and manufacturers both domestically and abroad.

The ASCII data files of the FARES database contain demographic and administrative information (DEMO), adverse event (REAC), drug information (DRUG), outcomes (OUTC), report sources (RPSR), therapy information (THER) and using indications (INDI).

A total of 13,649,428 reports were extracted from the FAERS database. According to the FDA's recommendations, a deduplication procedure was performed to select the latest FDA_DT with the same CASEIDs and select the higher PRIMARYID when the CASEID and FDA_DT were the same, resulting in 1,145,704 reports. According to the PRIMARYID of the deduplicated DEMO data, the DRUG and REAC data were deduplicated as well.

2.2 Adverse event and drug identification

All 21 preferred terms (PTs) describing adverse events, such as “Pancreatitis relapsing” and “Pancreatitis acute”, in the REAC files were investigated using the Medical Dictionary for Regulatory Activities(MedDRA) V23.0 and the Standardised MedDRA Queries (SMQ) term “acute pancreatitis” (SMQ: 20000022).

Drug names can be input arbitrarily in the FAERS database; therefore, MICROMEDEX® (Index Nominum) was utilized as a dictionary for the names of PIs (Table 1). Both generic names and brand names were used as keywords for FAERS database retrieval.

Table 1: Summary of FDA-approved protease inhibitors

Generic name	Brand name	Approval year
Atazanavir	Reyataz®	2003
Atazanavir/cobicistat	Evotaz®	2015
Amprenavir	Agenerase®	1999
Fosamprenavir	Lexiva®, Telzir®	2003
Nelfinavir	Viracept®	1997
Saquinavir	Fortovase®, Invirase®	1995
Tipranavir	Aptivus®	2005
Indinavir	Crixivan®	1996
Darunavir	Prezista®	2007
Darunavir/cobicistat	Rezolsta®, Prezcobix®	2014
Darunavir/cobicistat/emtricitabine/tenofovir	Symtuza®	2018
Ritonavir	Norvir®	1996
Ritonavir/lopinavir	Kaletra®	2001
Ritonavir/dasabuvir/ombitasvir/paritaprevir	Holkira®, Viekira®	2014
Ritonavir/ombitasvir/paritaprevir	Technivie®	2015

2.3 Data mining

The disproportionality analysis (the reporting odds ratio, ROR and the proportional reporting ratio, PRR) and the Bayesian analysis (the Bayesian confidence propagation neural network, BCPNN and the multi-item gamma Poisson shrinker, MGPS) algorithms were used to identify statistical associations between a drug and an adverse event (Table 2) [26-34]. In this study, adverse events were extracted when at least 1 of 4 indices met the criteria.

Table 2: Summary of Major Algorithms Used for Signal Detection

Algorithms	Equation	Criteria
ROR	$ROR=(a/b)/(c/d)$	95% CI>1, N≥2
	$95\%\ CI=e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	
PRR	$PRR=(a/(a+c))/(b/(b+d))$	PRR≥2, χ^2≥4, N≥3
	$\chi\ 2=\Sigma((O-E)2/E)$; (O=a,E=(a+b)(a+c)/(a+b+c+d))	
BCPNN	$IC=\log_2 a(a+b+c+d)/((a+c)(a+b))$	IC025>0
	$IC025=e^{\ln(IC)-1.96(1/a+1/b+1/c+1/d)^{0.5}}$	
MGPS	$EBGM=a(a+b+c+d)/((a+c)(a+b))$	EBGM05>2, N>0
	$EBGM05=e^{\ln(EBGM)-1.64(1/a+1/b+1/c+1/d)^{0.5}}$	

Abbreviations: a: number of reports containing both the suspected drug and the suspected adverse drug reaction; b: number of reports containing the suspected adverse drug reaction with other medications (except the drug of interest);. c: number of reports containing the suspected drug with other adverse drug reactions (except the event of interest); d: number of reports containing other medications and other adverse drug reactions; ROR: reporting odds ratio; CI: confidence interval; N: number of cooccurrences of PI use and AP; PRR: proportional reporting ratio; χ2: chi-squared; BCPNN: Bayesian confidence propagation neural network; IC: information component; IC025: the lower limit of the 95% two-sided CI of the IC; MGPS: multi-item gamma Poisson shrinker; EBGM: empirical Bayesian geometric mean; EBGM05: the lower 90% one-sided CI of EBGM

The associations between AP and different PI regimens were compared. The time to onset of AP was evaluated for each PI regimen. It was defined as the interval between the EVENT_DT (adverse event onset date) and the START_DT (start date of PI use). However, reports with input error (an EVENT_DT earlier than the START_DT) or inaccurate date entry were excluded. In addition, reports with fatal events attributed to drug toxicity were counted, and the fatality rate was calculated as the number of fatal events divided by the total number of events of AP associated with each PI regimen.

2.4. Statistical analysis

Descriptive analysis was used to summarize the clinical characteristics of the patients with PI-associated AP collected from the FAERS database. The times to onset of PI-associated AP between different PI regimens were compared using nonparametric tests (the Mann-Whitney test for dichotomous variables and the Kruskal-Wallis test when there were more than two subgroups of respondents) because the data were not normally distributed. Fatality rates were compared among different PI regimens using Pearson's chi-square test. The statistical significance was determined at $p < 0.05$ with 95% confidence intervals. Data mining and all statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

3.1 Descriptive analysis

33,832 adverse events related to PIs and 51,883 reports related to AP were recorded in the FAERS database between January 2004 and December 2019. Among them, PIs were set as the suspected drugs that caused AP in 285 reports, and the clinical characteristics of these patients are presented in Table 3.

Table 3: Clinical characteristics of patients with protease inhibitor-associated acute pancreatitis collected from the FAERS database

Characteristics	Reports, no. (%)
Reporting region	
North America	115 (40.35)
Europe	88 (30.88)
Asian	19 (6.67)
Oceania	9 (3.16)
South America	4 (1.4)
Africa	1 (0.35)
Unknown or missing	49 (17.19)
Reporters	
Health-care professional	205 (71.93)
Non-health-care professional	42 (14.74)
Unknown or missing	38 (13.33)
Reporting year	
2001-2005	58 (20.35)
2006-2010	87 (30.53)
2011-2015	65 (22.81)
2016-2019	74 (25.96)
Unknown or missing	1 (0.35)
Patient gender	
Male	184 (64.56)
Female	81 (28.42)
Unknown or missing	20 (7.02)
Patient age group (years)	
<18	2 (0.70)
18-44	71 (24.91)
45-64	80 (28.07)
>64	34 (11.93)
Unknown or missing	98 (34.39)
Suspected PI drug	
Atazanavir	52 (18.25)
Atazanavir/cobicistat	(0)
Amprenavir	2 (0.7)
Fosamprenavir	10 (3.51)
Nelfinavir	5 (1.75)
Saquinavir	4 (1.4)
Tipranavir	7 (2.46)
Indinavir	8 (2.81)
Darunavir	26 (9.12)
Darunavir/cobicistat	2 (0.7)
Darunavir/cobicistat/emtricitabine/tenofovir	1 (0.35)
Ritonavir	54 (18.95)
Ritonavir/lopinavir	48 (16.84)
Ritonavir/dasabuvir/ombitasvir/paritaprevir	64 (22.46)

Ritonavir/ombitasvir/paritaprevir	2 (0.7)
Indications	
HIV infection	171 (64.77)
Hepatitis C and hepatic cirrhosis	66 (25)
Unknown or missing	27 (10.23)

Data are number (%). PI: protease inhibitor; FAERS: Food and Drug Administration's Adverse Event Reporting System

The highest number of AP reports was associated with ritonavir/dasabuvir/ombitasvir/paritaprevir (n=64, 22.46%), followed by ritonavir (n=54, 18.95%), atazanavir (n=52, 18.25%), lopinavir/ritonavir (n=48, 16.84%), and darunavir (n=26, 9.12%). AP adverse events were most reported in HIV-infected patients (64.77%). Of these events, 64.56% occurred in men, and 28.42% occurred in women; the gender was unknown in 7.02% of the events. All but two events involved adult patients (aged > 18 years), and the average age was 49.67 years. Most of the cases were from North America (40.35%) and Europe (30.88%) and were mainly submitted by health care professionals (71.93%).

3.2. Disproportionality analysis and Bayesian analysis

No cooccurrence of atazanavir/cobicistat use and AP was reported, and only 1 and 2 cooccurrences of PI use and AP were reported for darunavir/cobicistat/emtricitabine/tenofovir and darunavir/cobicistat, respectively. Overall, according to the criteria for the 4 algorithms, 12 out of 15 PIs (all except the ones mentioned above) were suggested to be associated with AP. Lopinavir/ritonavir, ritonavir, nelfinavir, and darunavir, which are potential therapeutics for COVID-19, appeared to be associated with AP. The results are listed in Table 4. Among all PI therapies, indinavir was notably associated with AP because it had the highest ROR, PRR, IC, and EBGM.

Table 4: Disproportionality analysis and the Bayesian analysis of associations of different protease inhibitor regimens with acute pancreatitis

PI regimens	N	ROR (95% two-sided CI)	PRR (χ^2)	IC (95% one-side CI)	EBGM (95% one-side CI)
Atazanavir	52	3.01 (2.29,3.96)	2.99 (68.9)	1.58 (1.2)	2.98 (2.37)
Atazanavir/cobicistat	0	-	-	-	-
Amprenavir	2	3.89 (0.96,15.75)	3.84 (4.22)	1.94 (0.48)	3.84 (1.19)
Fosamprenavir	10	4.14 (2.22,7.74)	4.08 (23.38)	2.03 (1.09)	4.08 (2.42)
Nelfinavir	5	1.97 (0.82,4.75)	1.96 (2.37)	0.97 (0.4)	1.96 (0.94)
Saquinavir	4	2.26 (0.84,6.05)	2.25 (2.78)	1.17 (0.44)	2.25 (0.99)
Tipranavir	7	2.66 (1.26,5.6)	2.64 (7.15)	1.4 (0.66)	2.64 (1.41)
Indinavir	8	4.6 (2.29,9.27)	4.53 (22.11)	2.18 (1.08)	4.53 (2.52)
Darunavir	26	2.08 (1.41,3.06)	2.07 (14.37)	1.05 (0.71)	2.07 (1.5)
Darunavir/cobicistat	2	0.76 (0.19,3.05)	0.76 (0.15)	-0.39 (-)	0.76 (0.24)
Darunavir/cobicistat/emtricitabine/tenofovir	1	0.98 (0.14,6.97)	0.98 (0)	-0.03 (-)	0.98 (0.19)
Ritonavir	54	2.07 (1.58,2.71)	2.06 (29.61)	1.04 (0.8)	2.06 (1.65)
Ritonavir/lopinavir	48	2.19 (1.65,2.92)	2.18 (30.87)	1.13 (0.85)	2.18 (1.72)
Ritonavir/dasabuvir/ombitasvir/paritaprevir	64	1.1 (0.86,1.41)	1.1 (0.56)	0.14 (0.11)	1.1 (0.89)
Ritonavir/ombitasvir/paritaprevir	2	2.07 (0.52,8.35)	2.06 (1.1)	1.05 (0.26)	2.06 (0.64)

Abbreviations: PI: protease inhibitor; N: number of reports of PI-associated acute pancreatitis; ROR: reporting odds ratio; CI: confidence interval; PRR: proportional reporting ratio; χ^2: chi-squared; IC: information component; EBGM: empirical Bayes geometric mean

3.3. Time to onset of PI-associated AP

The overall median time to event onset of PI-related AP was 103 (interquartile range [IQR]: 26–408) days. For ritonavir, lopinavir/ritonavir, darunavir and nelfinavir, the median times to onset were 177 (IQR: 56-539) days, 91 (IQR: 22-352.5) days, 311 (IQR: 235-481.5) days and 918 (IQR: 469-2132) days, respectively. The times to onset associated with each PI regimen are shown in Fig. 1.

Fig. 1: Time to onset of acute pancreatitis associated with different protease inhibitor regimens (Pearson's chi-square test, *P*=0.0048)

Interestingly, in some reports, AP-related adverse events occurred as soon as after the first dose of several PIs, including atazanavir, ritonavir, lopinavir/ritonavir and ritonavir/dasabuvir/ombitasvir/paritaprevir. There were significant differences in the times to onset among these PI therapies (p=0.0048). Patients treated with ritonavir/dasabuvir/ombitasvir/paritaprevir appeared to have an earlier onset of AP than those receiving atazanavir (31 [IQR: 17–68.25] days vs 187.5 [IQR: 80.5–556.5] days, p=0.0379) or ritonavir (31 [IQR: 17–68.25] days vs 177 [IQR: 56–539] days, p=0.0371).

3.4. Fatality due to PI-associated AP

To evaluate the prognosis of AP after PI use, we assessed fatality rates due to AP-related adverse events following various PI regimens, and the results are shown in Table 5. Fatalities occurred in 38 (14.02%) of 271 reported PI-induced AP cases. There was no significant difference in fatality rates across different PI regimens (Pearson's chi-square test for overall comparisons, p=0.730).

Table 5: Fatality rates due to acute pancreatitis adverse events following various protease inhibitor regimens

Drug	Death (N)	Number of Reports	Fatality (%)
Atazanavir	6	52	11.54
Atazanavir/cobicistat	-	-	-
Amprenavir	0	2	0
Fosamprenavir	0	8	0
Nelfinavir	1	5	20
Saquinavir	1	4	25
Tipranavir	0	3	0
Indinavir	1	8	12.5
Darunavir	2	26	7.69
Darunavir/cobicistat	0	2	0
Darunavir/cobicistat/emtricitabine/tenofovir	0	1	0
Ritonavir	10	53	18.87
Ritonavir/lopinavir	10	44	22.73
Ritonavir/dasabuvir/ombitasvir/paritaprevir	6	61	9.84
Ritonavir/ombitasvir/paritaprevir	1	2	50

Data are number or percentage, as appropriate

Discussion

Since the outbreak of COVID-19, there have been more than 5204,000 confirmed cases globally, and 337,687 people have lost their lives[1]. Thousands more are fighting for their lives in hospitals. The World Health Organization (WHO) has characterized COVID-19 as a pandemic. All countries activated and scaled up their emergency response mechanisms, and a great deal of effort has been made to identify effective drugs against the virus. Some PIs, such as lopinavir/ritonavir and darunavir/cobicistat, have been tested in clinical trials in China. This study focused on the occurrence, timing, and prognosis of AP following the use of various PI regimens in real-world practice based on the FAERS pharmacovigilance database. First using disproportionality analysis and

Bayesian analysis as a rapid and effective signal detection method to perform the largest-to-date postmarketing surveillance of these PIs, we attempted to provide valuable and timely signals for clinical evaluation to minimize the potential harm induced by AP in the treatment of COVID-19. The study showed that 12 out of the 15 studied PIs, including lopinavir/ritonavir, darunavir, and nelfinavir, which are potential therapeutics for COVID-19, were associated with AP-related adverse events.

Despite the potential benefits it provides to COVID-19 patients, the use of PIs may be accompanied by serious side effects, including AP. Two case reports[23, 24]have suggested a causal mechanism between PI-induced hypertriglyceridemia and AP, while a third case report of PI-associated acute pancreatitis was not associated with a rise in serum triglycerides[25]. It remains unclear whether PIs are associated with pancreatitis. Hence, it is important to recognize the associations between particular PI regimens and AP as well as the clinical features and develop an awareness of this adverse event among practitioners prescribing PI for the treatment of COVID-19 and other professionals, such as pharmacists and nurses. However, the assessment of PI-associated AP is quite challenging because of its low incidence and overlooked manifestations[21, 22]. Due to strict study entry criteria, relatively small sample sizes, and a finite scope and time frame, it is difficult to achieve this goal through experimental studies, including mandatory clinical trials, alone. Performing postmarketing surveillance is an efficient way to discover rare but potentially severe adverse reactions and help us acquire vital basis for prevention. Therefore, our study provides a profile of PI-associated AP through data mining of 33,832 adverse events related to PIs documented in the FAERS database.

Some prior studies that included patients receiving HAART found an association between female gender and AP and hypothesized that a smaller body weight might increase the toxicity of nucleotide reverse-transcriptase inhibitors (NRTIs) [35, 36]. However, Manfredi et al. found no association between gender and the risk of AP related to PI-based HAART exposure[21]. In our study, based on reports from the FAERS database, we found that PI-associated AP seemed to predominately affect men rather than women (64.56% vs. 28.42%). Most of these collected reports were from North America (40.35%) and Europe (30.88%), where women make up a smaller proportion of the HIV patient population[37]. Therefore, we could not conclude that men are more likely than women to suffer from AP following PI regimens. Further research is required to reevaluate the relationship between gender and PI-associated AP.

Guo et al. found that advanced age is a risk factor for acute pancreatitis after a retrospective cohort study of 4,972 patients with HIV infection, in which they found 159 cases of AP[38]. Conversely, we did not observe that PI-induced AP predominately affected elderly patients (11.93% of patients ≥65 years vs. 53.68% of patients < 65 years). On account of a lack of information in the FAERS database, it was difficult to control confounding factors such as age in this study. Further research is needed to explore the association between advanced age and the incidence of PI-related AP.

Previous studies have reported conflicting results regarding the impact of PIs on the development of pancreatitis[16]. Most evidence supporting the causal relationship of AP to PIs has come from case reports[23-25] and is insufficient to provide an overview of the risk of rare adverse events such as AP. Riedel et al. found that neither PI nor non-nucleoside reverse-transcriptase inhibitors (NNRTIs) are associated with an increased rate of AP through a ten-year cohort study[39]. Conversely, based on this pharmacovigilance analysis, 12 out of the 15 studied PIs were found to be associated with AP-related adverse events, which is similar to what was reported in some prior studies[21, 22]. Hypertriglyceridemia has been demonstrated to cause pancreatitis[40, 41]. According to previous studies, all available PIs are associated with significant increases in plasma triglyceride concentrations[42, 43], but hypertriglyceridemia is more frequently observed following the use of ritonavir or lopinavir/ritonavir combination therapy than following other PI-based combinations[44, 45]. Due to their potential clinicopathological consequences, ritonavir and lopinavir/ritonavir regimens may lead to an increased risk of hyperlipidemic pancreatitis[42, 46]. Surprisingly, we observed that indinavir, not ritonavir, seemed to have the strongest association with AP among all PI regimens, including ritonavir and lopinavir/ritonavir. This may be due to the relatively limited cases of AP-associated indinavir reported (8 reports). In our study, the 64.77% of reported cases are involving HIV-infected patients. As we know, antiretroviral treatment is very complex and dangerous due to concomitant medications and their toxic effects, including drug-induced AP. There are plenty of factors which can affect the pancreas, such as a previous history of AP, hepatobiliary diseases, alcohol abuse, low CD4 counts, and opportunistic infection prophylaxis, in addition to direct lesions caused by HIV[16]. All these factors make the evaluation of the association between PI and AP more difficult.

Another finding was that the median time to the onset of AP was 103 (IQR: 26-408) days after the initiation of PI treatment, which was similar to the onset time observed in some previous case reports[23-25]. Ritonavir/dasabuvir/ombitasvir/paritaprevir appeared to have the earliest onset of AP (31 [IQR: 17–68.25] days) among all studied PI regimens. For ritonavir and lopinavir/ritonavir, the median times to onset were 177 (IQR: 56-539) days and 91 (IQR: 22-352.5) days, respectively. It was suggested that ritonavir-based PI regimens may induce AP earlier than other PI regimens. Although the onset of AP after the use of PI seemed to be long according to some reports collected in this study, AP could occur as soon as after the first several doses of the ritonavir-based PI regimens mentioned above and atazanavir. Notably, triple combination therapy with ritonavir/lopinavir, ribavirin and interferon-alpha has been recommended as a drug treatment option by the guidelines, and it might be predominantly used to treat COVID-19 patients. However, both interferon monotherapy and interferon/ribavirin combination therapy have been reported in the literature to be causally associated with AP[47-48]. As a consequence of the multifactorial effects, triple combination therapy may lead to an increased risk of AP. Patients receiving PI regimens or the recommended triple combination therapy for the treatment of COVID-19 should be closely observed. Drug-induced AP should be considered, if patients present with clinical signs and symptoms of pancreatitis, including abdominal pain, nausea, vomiting, and conjunction with abnormal levels of serum lipase or/and amylase.

We also assessed and compared the fatality rates of AP associated with PIs to investigate differences in the severity of AP associated with various PIs. It was observed that AP was generally associated with poor outcomes, exhibiting a fatality rate of 14.02%, which was more than two times that found by Riedelet al. in a cohort study that followed 5,970 HIV-infected patients[39]. In that study, five patients died of pancreatitis during their hospitalization, yielding an in-hospital mortality rate of 5.9% for AP. As there is no consensus definition of acute pancreatitis, the different inclusion criteria used in the two studies may have resulted in different specificities and sensitivities of case inclusion. This may have caused the difference between the fatality rates in the two studies. Furthermore, we found that among all 271 reported PI-induced AP cases, compared with the other PIs, ritonavir (18.87%) and lopinavir/ritonavir (22.73%) appeared to be associated with a higher risk of death. However, based on the collected data, there was no significant difference in fatality rates across different PI regimens

(Pearson's chi-square test for overall comparison, p=0.730). Fatal events occurred in 1 (25.00%) of 4 patients treated with saquinavir and 1 (20.00%) of 5 patients treated with nelfinavir; however, there were not enough cases reported to draw a conclusion, and continued surveillance is needed.

Based on spontaneous reporting systems (SRSs), disproportionality analysis and Bayesian analysis allow for signal detection rapidly and generate hypothesis about associations between AP and various PI regimens. However, it should be noted that in addition to many advantages, data mining techniques used in this study still have several limitations. First, affected by the inherent limitation of SRSs, sources of AP reports are non-homogeneous. Incomplete reporting, underreporting, false reporting, and inaccuracy might result in reporting bias and even misleading[49]. Second, owing to a lack of insufficient information in the FAERS database, the possibility of verification of the clinical findings justifying the reported AP is quite limited, and it is also scarcely possible to control such confounding factors as indications, pre-existing pancreatic diseases, comorbidities or other factors which might have an impact on AP occurrence[50]. Third, as reports extracted from the FAERS database do not reflect the total number of adverse reactions involving AP, the number of reports for a particular PI may be influenced by the extent of use of the product, which may be affected by some factors such as enterprise publicity and product price[49,50]. It cannot be used to quantify the incidence of PI-associated AP. Data mining techniques only provide a profile of PI-associated AP through signal detection. It is generally insufficient to prove the causal relationship, which needs to be replicated ideally by prospective studies[51].

Conclusion

Based on real-world practice data, this pharmacovigilance study identified associations between AP and various PI regimens, including lopinavir/ritonavir, darunavir and nelfinavir, which are potential therapeutics for COVID-19. Indinavir appeared to have a stronger association with AP than other PIs. Moreover, AP associated with ritonavir boosted regimens had an earlier onset and occurred as soon as after the first several doses in some cases. Further pharmacoepidemiological studies should continue to evaluate the hypotheses generated by this study. Our findings provide a foundation for continued surveillance and investigation into this matter.

Not only patients receiving long-term PI treatment, but also those receiving PI regimens for the short –term treatment of COVID-19 should be closely observed.

List Of Abbreviations

PI: Protease inhibitor

AP: Acute pancreatitis

FAERS: Food and Drug Administration's Adverse Event Reporting System

ADR: Adverse drug reaction

COVID-19: Coronavirus disease 2019

HARRT: Highly active antiretroviral therapy

HIV: Human immunodeficiency virus

SARS-CoV:Severe acute respiratory syndrome coronavirus

MERS-CoV: Middle East respiratory syndrome coronavirus

ROR: Reporting odds ratio

PRR: Proportional reporting ratio

BCPNN: Bayesian confidence propagation neural network

MGPS: Multi-item gamma Poisson shrinke

IQR: Interquartile range

NRTI: Nucleotide reverse-transcriptase inhibitor

NNRTI: Non-nucleoside reverse-transcriptase inhibitor

SRS: Spontaneous reporting system

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Figures

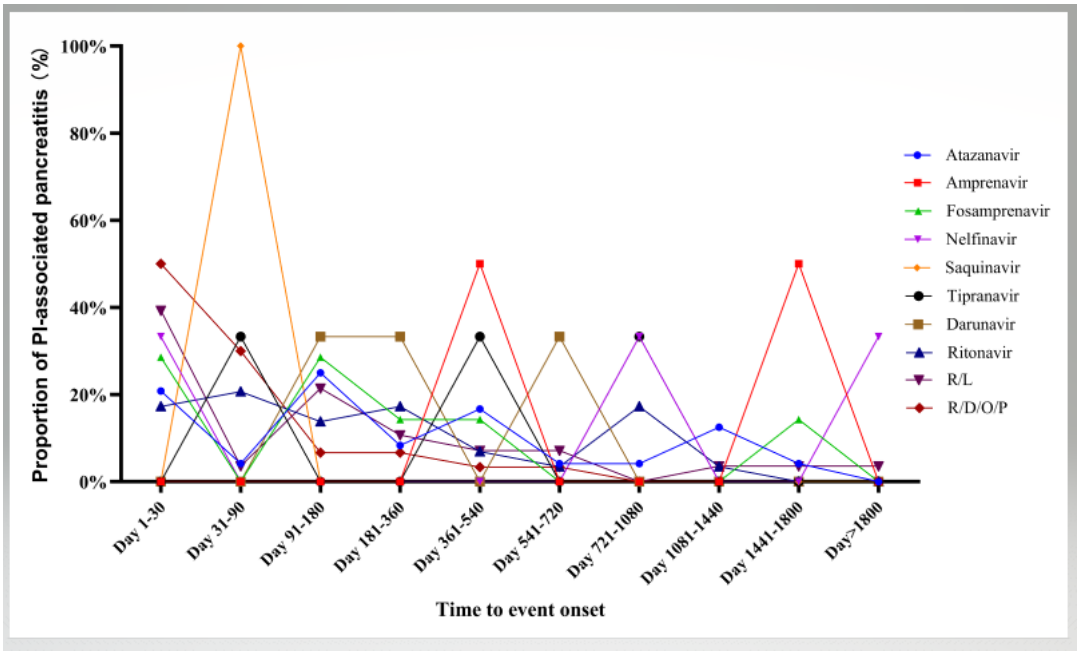

Figure 1

Time to onset of acute pancreatitis associated with different protease inhibitor regimens (Pearson's chi-square test, P=0.0048)