



Current usage status of somatostatin and its analogs and trypsin inhibitors: a real-world study of 34,654 Chinese adult patients with acute pancreatitis

Xufeng Mao¹, Zhangwei Yang²

¹Department of Pharmacy, Changhai Hospital, The Second Military Medical University, Shanghai, China; ²Department of Information, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: Z Yang; (II) Administrative support: Z Yang; (III) Provision of study materials or patients: Z Yang; (IV) Collection and assembly of data: X Mao; (V) Data analysis and interpretation: X Mao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhangwei Yang, PhD. Department of Information, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, No. 1878 North Sichuan Road, Hongkou District, Shanghai 200081, China. Email: shdsyy_yzw@sina.com.

Background: Although somatostatin and its analogs and trypsin inhibitors (TSI) are widely recommended for acute pancreatitis (AP), there is a lack of high-quality multicenter trials that validate these drug classes. We aimed to examine the current usage status of somatostatin and its analogs and TSI in Chinese adult AP patients.

Methods: We conducted a retrospective study which collected information for adult patients who were diagnosed with AP from January 1, 2015 to June 30, 2017 at 192 hospitals in China. Subsequently, we conducted a statistical analysis of the baseline information of patients, and revealed the usage of somatostatin, octreotide, ulinastatin, and gabexate. Thereafter, we stratified AP by severity and analyzed the current status of treatment.

Results: A total of 34,654 patients were included in this study. Mean age of patients was 49.9 years and 63% were males. Fifty-five percent of mild AP patients opted to receive octreotide, while 53.66% and 64.61% of moderate AP and severe AP patients respectively opted to receive somatostatin. At treatment initiation, somatostatin was mainly prescribed for mild and moderate AP patients, which were 723 and 894 daily defined doses (i.e., defined dose per day for a drug used by every 1,000 patients). Ulinastatin was mainly prescribed for severe AP patients, with a prescription volume of 1,230 daily defined doses. The consumption of ulinastatin in later stages of severe AP treatment was significantly greater than other drugs.

Conclusions: Somatostatin analogs and TSI are widely used as therapeutic drugs for AP treatment in China, with usage beginning at the early stages of the disease and lasting on average for 1 week. Of these drugs, somatostatin and octreotide were identified as the most commonly-used drugs, while ulinastatin was found to be widely used at the late stages of severe AP.

Keywords: China; pancreatitis; somatostatin; octreotide; trypsin inhibitors (TSI)

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Introduction

Acute pancreatitis (AP) refers to auto-digestion of the pancreas, where pancreatic enzymes injure the pancreatic tissue, leading to dysfunction of the gland, remote organs, and systems. Globally, the annual incidence of AP is 34 per 100,000 people (1) and continues to increase yearly. From 2006 to 2014, its annual incidence increased by 18%. AP is currently one of the most common gastrointestinal disorders that cause hospitalization in the US and costs the health care system \$9.3 billion annually. To add, ~30,000 inpatients are reported in the US every year, with 2.64 billion USD of medical expenses being paid every year (2-4). According to the International 2012 Revised Atlanta Classification for Acute Pancreatitis, AP is mainly classified as mild (MAP), moderate (MSAP), and severe (SAP) (5). Common etiologies include cholelithiasis (including biliary microlithiasis), hypertriglyceridemia, and alcohol consumption. In China, biliary pancreatitis is the primary etiology of AP (6). Currently, supportive treatment is usually employed as initial treatment for AP patients and includes fluid resuscitation, pain control, nutrition support, and maintenance of organ function.

For the use of AP drugs that inhibit exocrine secretion by the pancreas and inhibit trypsin, somatostatin and its analogs (SSTA) and trypsin inhibitors (TSI) are currently mainly used in clinical practice. SSTA (somatostatin, octreotide) can directly inhibit exocrine secretion by the pancreas while TSI drugs (ulinastatin, gabexate) can broadly inhibit the secretion and activity of trypsin, elastase, phospholipase A, and other hydrolases that are associated with AP progression. TSI can also stabilize lysosome membranes, improve pancreatic microcirculation, and reduce the occurrence of AP complications.

China has a large population and a high number of AP patients. Therefore, physicians have ample experience in the use of drugs to treat AP. SSTA and TSI drugs are recognized by many physicians for the clinical treatment of AP, and China's authoritative guidelines and consensus have recommended these two treatment methods (6,7). The results of previous studies showed that TSI drugs can effectively reduce the mortality of AP patients (8,9). However, most of the selected studies are retrospective cohort studies and case-control studies, and there is a lack of high-quality multicenter randomized controlled trials to further validate these drug classes. Epidemiological data and studies on the current status of drug treatment of AP are outdated. The age of onset of AP, comorbidities, clinical

pathway, drug treatment protocol, and hospitalization costs are intimately associated with patient outcomes and financial burden. Because of the aforementioned reasons, Changhai Hospital attempted to collect real-world study data on AP diagnosis and treatment from many hospitals in China to carry out mining and analysis of the disease characteristics of AP patients in China and real-world utilization status of SSTA and TSI drugs to provide a real-world basis and reference for rational drug administration for AP by clinicians.

We present the following article in accordance with the STROBE Reporting Checklist (available at <http://dx.doi.org/10.21037/apm-19-363>).

Methods

Study design

We conducted a retrospective study base on a large medical database in Changhai Hospital, Shanghai. A cohort of all patients admitted to the hospitals in this database, from January 1, 2015 to June 30, 2017, was investigated.

Aim of the study

Herein, we aimed to examine the current usage status of SSTA and TSI in Chinese adult AP patients.

Data source

Data were obtained from the research service platform database of Changhai Hospital which has the electronic medical records of 15 million inpatients every year. These patients were from 192 general hospitals in China. Data that are accessible for every patient included demographic data (age, sex, medical insurance), hospital characteristics (number of beds, region, grade, and teaching status), discharge diagnosis [primary diagnosis and other diagnosis, including name of diagnosis and international classification of diseases 10th version (ICD-10th) code], dosing record (name of drug, administration method and dose, and time), payment records (payment details and payment time), and records of surgeries and relevant tests and examinations. The main aim of constructing the database is to monitor drug resistance in the regional medical system. Previous studies on community-acquired pneumonia provided detailed descriptions and explanations of this database (10).

The study was conducted in accordance with the

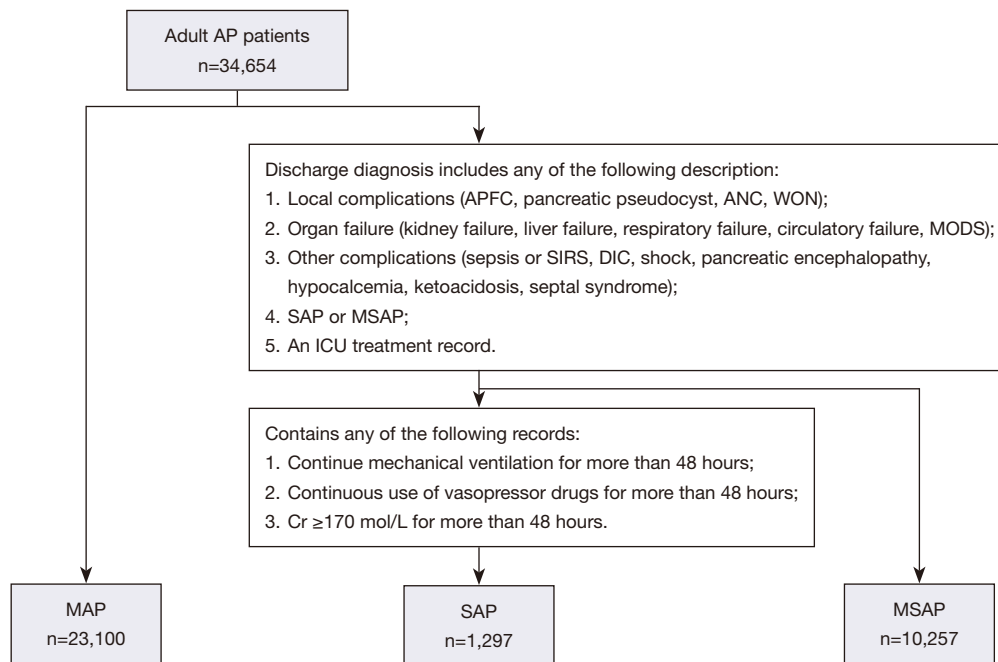


Figure 1 Flowchart of the study populations. AP, acute pancreatitis; MAP, mild acute pancreatitis; MSAP, moderate acute pancreatitis; SAP, severe acute pancreatitis; APFC, acute peripancreatic fluid collection; ANC, acute necrotic collection; WON, walled-off necrosis; MODS, multiple organ dysfunction syndrome; SIRS, systemic inflammation reaction syndrome; DIC, disseminated intravascular coagulation; ICU, intensive care unit; Cr, serum creatinine.

principles of the Declaration of Helsinki (as revised in 2013). All patients were anonymous and specific information that could be used for patient identification was not included, such as identification numbers and address. The review and approval of this study was exempted by the ethics committee of Changhai Hospital.

Study population and classification

We identified patients aged ≥ 18 with a primary discharge diagnosis of AP (ICD-10th: K85) from January 1, 2015 to June 30, 2017. To exclude the effects of daytime ward on the study, patients with a hospitalization length less than 3 days were excluded from the study.

The 2012 Revised Atlanta Classification for Acute Pancreatitis classified AP according to severity: mild AP (MAP, absence of organ failure and local or systemic complications), moderate AP (MSAP, transient organ failure or presence of local or systemic complications), and severe AP (SAP, persistent organ failure). However, not all electronic medical records in China state the severity of AP in the discharge diagnosis for every patient. Therefore,

we examined the discharge diagnosis for every patient and defined MAP as the absence of text description on local or systemic complications, organ failure, and moderate and severe pancreatitis in the discharge diagnosis and no record of intensive care unit transfer in the diagnosis process. The diagnosis description for local and systemic complications includes acute peri-pancreatic fluid collection, acute necrotic collection, walled-off necrosis, pancreatic pseudocyst, organ failure, sepsis, systemic inflammatory response syndrome, shock, pancreatic encephalopathy, disseminated intravascular coagulation, ketoacidosis, abdominal compartment syndrome, and hypocalcemia. In the remaining non-MAP patients, we defined SAP as patients who fulfilled any of the following criteria: serum creatinine $>170 \mu\text{mol/L}$ and persistence for more than 48 h, persistent mechanical ventilation for more than 48 h, and persistent usage of vasopressors for more than 48 h (Figure 1).

Study endpoints

The main focus of this study was to explore the application of SSTA and TSI drugs that are approved for marketing in

China for AP treatment. These drugs include somatostatin, octreotide, gabexate, and ulinastatin. Drug use-related markers include the utilization rate of drugs, number of days of drug usage, time of first dose (time from first use of drug to admission), and drug costs. We used the defined daily dose (DDD) for horizontal comparison of dosage between different drugs (11). Drug DDD values were mainly obtained from searching the World Health Organization website. If no drug-related information was available on the website, the package insert was used to determine daily dose. Finally, the DDD values for somatostatin, octreotide, gabexate, and ulinastatin were found to be 6, 0.7, 300 mg, and 300,000 units, respectively. The drug dose used during the period of time divided by the DDD of the drug is used to obtain the summary DDD (DDDs) for the period. Usually, DDDs represent the frequency of drug usage. During evaluation of the overall drug prescription volume, we used DDDs/1,000 patients/day (i.e., mean consumption of a drug every day in 1,000 patients). In addition, we defined drug utilization index (DUI) as the DDDs of a time period divided by the actual number of days of drug administration to measure the daily dose for each drug use. A DUI equal to 1 indicates that the actual usage of the drug conforms to the DDD recommended by World Health Organization.

Statistical analysis

Descriptive analysis was mainly used for data statistics. Data distribution was expressed as mean and 95% confidence interval (CI). If data were skewed, they were expressed as median and upper and lower quartiles. First, we described the baseline characteristics of all patients and baseline characteristics after stratification by severity (including age, sex, chronic comorbidity score, and hospital characteristics such as number of beds). The Charlson Comorbidity Index was used to evaluate chronic comorbidities which were converted to ICD-10th codes. Thereafter, drug usage status and treatment methods of somatostatin, octreotide, gabexate, and ulinastatin in patients with different disease severities (MAP, MSAP, and SAP) were examined. To add, drug usage trends in every quarter and prescription trends of all patients during the 30-day admission from 2015 to 2017 were evaluated. DUI and DDDs/1,000 patients/day were used to evaluate prescription trends. The combinations of these drugs in actual application as well as treatment regimens that are frequently used in clinical practice (monotherapy or combinational therapy) were evaluated.

All data in this study were processed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

We enrolled 34,654 adult patients from January 1, 2015 to June 30, 2017 that had a discharge diagnosis of AP. Of these patients, more than 60% were treated in large hospitals (bed number >1,000 beds). Mean age of patients was 49.94 years (95% CI: 49.76–50.11), 62.95% were male patients, median length of hospitalization was 10 days (IQR: 7–14), and hospital mortality rate was 0.35%. After patients were classified according to our definitions for AP severity, number of MAP, MSAP, and SAP patients was 23,100 (66.66%), 10,257 (29.60%), and 1,297 (3.74%), respectively. The stratified data revealed that SAP patients tend to seek medical attention in large hospitals, and mortality, length of hospitalization, and hospitalization costs significantly increased with older age and more severe chronic comorbidities (*Table 1*).

Study results

- (I) Time of first drug usage: for most AP patients, SSTA and TSI treatment began within 24 hours after admission and were less affected by disease severity.
- (II) Drug treatment: for drug selection, 55% of MAP patients received octreotide as initial treatment, while MSAP and SAP patients mainly selected somatostatin, with utilization rates of 53.66% and 64.61%, respectively. A greater proportion of patients with higher severity received ulinastatin and somatostatin.
- (III) Drug treatment duration: treatment duration for the 4 drugs were similar; however, duration was shorter in MAP patients (around 4 days) and longer in SAP patients (1 week).
- (IV) Drug therapeutic index: the therapeutic index of octreotide was lower than that of the other 3 drugs. When disease worsened in patients, the dose used for these drugs increased, particularly ulinastatin; the DUI of ulinastatin in SAP patients was 2.20, which exceeded the recommended dose by 2-fold (*Table 2*).
- (V) Most frequent medication combinations for different disease severities: for AP patients, physicians tended to employ SSTA monotherapy, such as octreotide or somatostatin (>40%). In addition, the combination of these two drugs with ulinastatin or in the absence of TSI is also an option. After AP worsens, physicians

Table 1 Characteristics of patients with acute pancreatitis after stratification

Category	All case (100.00%) (n=34,654)	MAP (66.66%) (n=23,100)	MSAP (29.60%) (n=10,257)	SAP (3.74%) (n=1,297)
Age (mean, 95% CI)	49.94 (49.76–50.11)	49.08 (48.87–49.30)	51.26 (50.95–51.57)	54.56 (53.70–55.60)
Male (%)	21,816 (62.95)	14,564 (63.05)	6,403 (62.43)	849 (65.46)
Hospital bed size (n, %)				
Small (<500 beds)	4,924 (14.21)	4,182 (18.1)	675 (6.58)	67 (5.17)
Medium (500–1,000 beds)	7,350 (21.21)	5,418 (23.45)	1,767 (17.23)	165 (12.72)
Large (>1,000 beds)	22,380 (64.58)	13,500 (58.44)	7,815 (76.19)	1,065 (82.11)
Charlson Comorbidity Index (mean, 95% CI)	0.75 (0.74–0.76)	0.58 (0.57–0.59)	1.05 (1.02–1.07)	1.37 (1.29–1.45)
Biliary pancreatitis (%)	13,748 (39.67)	8,675 (37.55)	4,607 (44.92)	466 (35.93)
Hospital mortality (%)	121 (0.35)	0	55 (0.54)	66 (5.09)
LOS (day, median, IQR)	10 [7–14]	9 [7–12]	12 [8–18]	16 [10–26]
Hospitalization costs (¥, median, IQR)	17,241.45 [10,055–30,999]	13,379.55 [8,353–20,927]	31,626.00 [18,885–51,730]	82,046.50 [36,816–168,691]

MAP, mild acute pancreatitis; MSAP, moderate severe acute pancreatitis; SAP, severe acute pancreatitis.

Table 2 Usage of trypsin inhibitor in patients with acute pancreatitis

Medicine	n	TFD (hour, median, IQR)	Utilization ratio (%)	Medication duration (day, median, IQR)	DUI	
MAP	Somatostatin	10,408	5.81 (2.27–16.39)	45.06	4 [2–6]	1.19
	Octreotide	12,893	7.81 (2.68–22.38)	55.81	4 [3–6]	0.96
	Ulinastatin	6,157	6.01 (2.24–17.52)	26.65	4 [3–7]	1.13
	Gabexate	5,105	5.58 (2.35–17.74)	22.10	5 [3–7]	1.19
MSAP	Somatostatin	5,504	6.28 (2.23–17.44)	53.66	5 [3–8]	1.22
	Octreotide	5,560	13.27 (3.54–49.91)	54.21	6 [3–9]	0.96
	Ulinastatin	4,140	5.60 (2.30–18.99)	40.36	6 [3–10]	1.43
	Gabexate	2,610	7.37 (2.67–20.45)	25.45	6 [3–9]	1.39
SAP	Somatostatin	838	7.24 (2.30–19.98)	64.61	6 [3–11]	1.20
	Octreotide	695	17.79 (4.36–126.79)	53.59	7 [4–12]	1.04
	Ulinastatin	642	5.99 (2.35–22.21)	49.50	7 [4–13]	2.20
	Gabexate	410	9.26 (2.55–21.64)	31.61	6 [3–10]	1.76

TFD, time from admission to the time of the first dose; DUI, Drug Utilization Index, computed as follows: summary DDD divided by actual days of medication; DDD, defined daily dose; MAP, mild acute pancreatitis; MSAP, moderate severe acute pancreatitis; SAP, severe acute pancreatitis.

tended to combine SSTAs and TSIs and somatostatin or octreotide. To add, ulinastatin is usually the most common option for SAP patients (>30%) (Table 3).

(VI) Analysis of the temporal trends of consumption and

drug utilization rates of different drug prescriptions: by examining the prescription volume (expressed as DDDs/1,000 patients/day) for every quarter from January 1, 2015 to June 30 2017, we found that drug

Table 3 Top 5 trypsin inhibitor regimens for patients with acute pancreatitis after stratification

Rank	All case (n=34,654)		MAP (n=23,100)		MSAP (n=10,257)		SAP (n=1,297)	
	Regimen	n (%)	Regimen	n (%)	Regimen	n (%)	Regimen	n (%)
1	O	8,002 (23.09)	O	6,142 (26.59)	O	1,727 (16.84)	S	184 (14.19)
2	S	5,689 (16.42)	S	4,143 (17.94)	S	1,362 (13.28)	S+U	149 (11.49)
3	O+U	3,257 (9.40)	O+U	2,036 (8.81)	S+U	1,311 (12.78)	O+U	144 (11.10)
4	S+U	3,065 (8.84)	Null	1,916 (8.29)	O+U	1,077 (10.50)	S+O+U	138 (10.64)
5	Null	2,768 (7.99)	S+U	1,605 (6.95)	Null	780 (7.60)	O	133 (10.25)

S, somatostatin; O, octreotide; U, ulinastatin; Null, not used; MAP, mild acute pancreatitis; MSAP, moderate severe acute pancreatitis; SAP, severe acute pancreatitis.

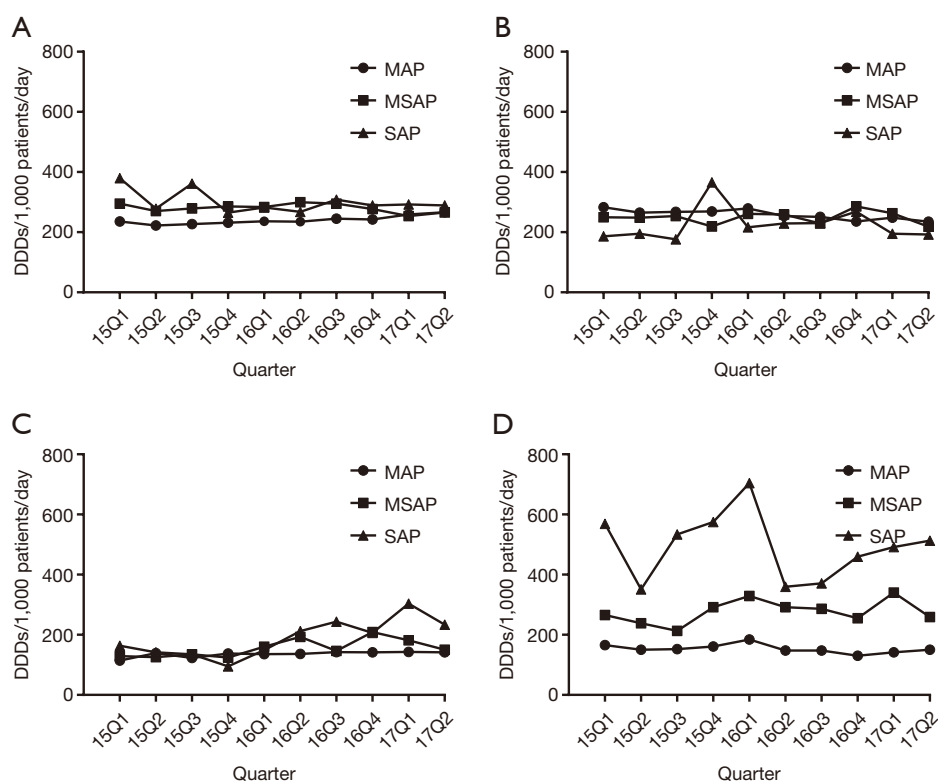


Figure 2 Prescriptions of trypsin inhibitor medications by quarter from January 2015 to June 2017. (A) Somatostatin; (B) octreotide; (C) gabexate; (D) ulinastatin. DDD, defined daily dose.

consumption for MAP and MSAP was relatively constant compared to that for SAP patients. To add, ulinastatin was found to differ from the other drugs as its prescription consumption was more significant with different disease severities, and its use in SAP patients was significantly higher than that for other drugs. For the temporal trend for utilization rate, with the exception of gabexate in SAP patients, the

usage of other drugs was relatively stable during the 2.5-year observation period. Similarly, we observed that the utilization rate of somatostatin and ulinastatin changed with disease severity (*Figures 2, 3*).

(VII) Drug usage dynamic changes during hospitalization: lastly, we classified the daily drug usage status for every patient during hospitalization. Thereafter, patient data were grouped according to their length

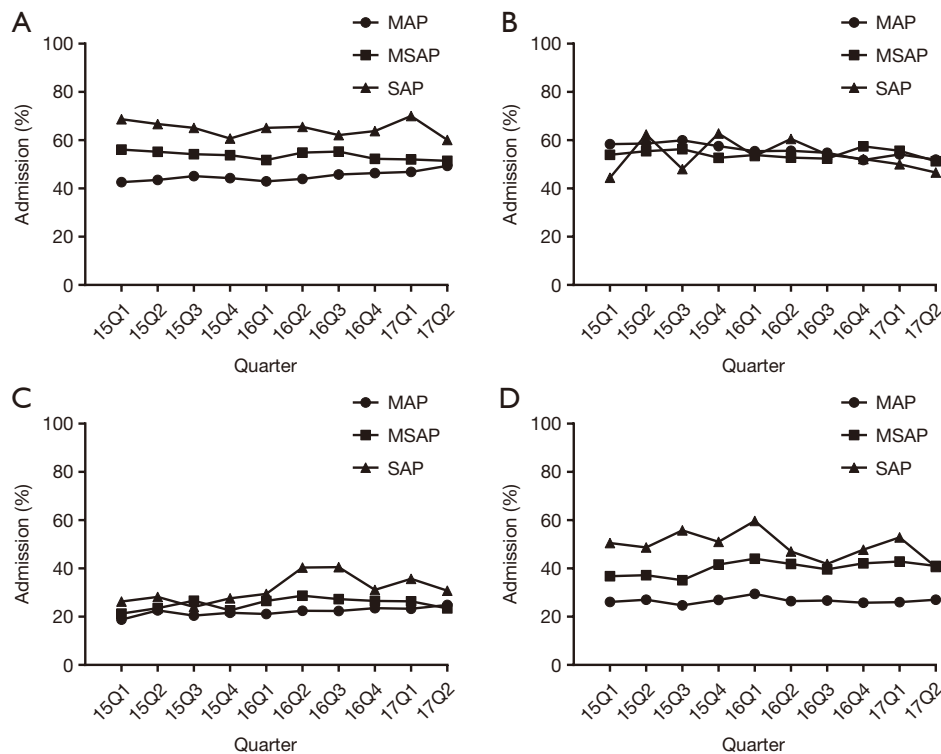


Figure 3 Utilization ratio of trypsin inhibitor medications in patients with acute pancreatitis by quarter from January 2015 to June 2017. (A) Somatostatin; (B) octreotide; (C) gabexate; (D) ulínastatin.

of hospitalization (e.g., all patients were hospitalized on Day 1, and study subject was TSI usage status of 34,654 patients on Day 1) and prescription volume of physicians was determined. Among MAP and MSAP patients, the drug with the highest initial prescription volume was somatostatin, with a prescription volume of 723 and 894 DDDs/1,000 patients/day, respectively. In SAP patients, the drug with the highest initial prescription volume was ulínastatin, with a prescription volume of 1,230 DDDs/1,000 patients/day. As treatment duration increased, the consumption of all drugs showed a decreasing trend. However, the consumption of ulínastatin at the later stages of SAP treatment was significantly higher than that of any other drug, which was maintained at 300–400 DDDs/1,000 patients/day (Figure 4).

Discussion

Stratification by AP characteristics and severity

To conduct this study, we used the national database of

China to explore the disease characteristics and current status of major drugs for AP in China. Currently, only few large-scale studies on AP exists in China and to our knowledge, this is the first epidemiological study with more than 10,000 AP patients in China. Based on our study results, mean age (SD) of AP patients in China is 49.9 (16.5) years, a value slightly lower than that of most European countries. To add, 63% of patients were males, a value higher than that found for US patients (47%) (12). AP was identified to be caused by cholelithiasis in 40% of patients, which is similar to the ratio reported in other studies (13). In the present study, median hospital mortality rate and length of hospitalization were 0.35% and 10 days, respectively, and in the US, the values were 0.7% and 3 days, respectively (2). Although the length of hospitalization of Chinese patients was longer than that of most countries, the single hospitalization cost of these patients was lower than that for developed countries (median hospitalization cost was 17,241 CNY, which is equivalent to 2,597 US dollars. In 2014, median hospitalization cost was 6,240 US dollars in the US), and hospital mortality rate was lower than the data reported in other countries. Because of the effects of outside

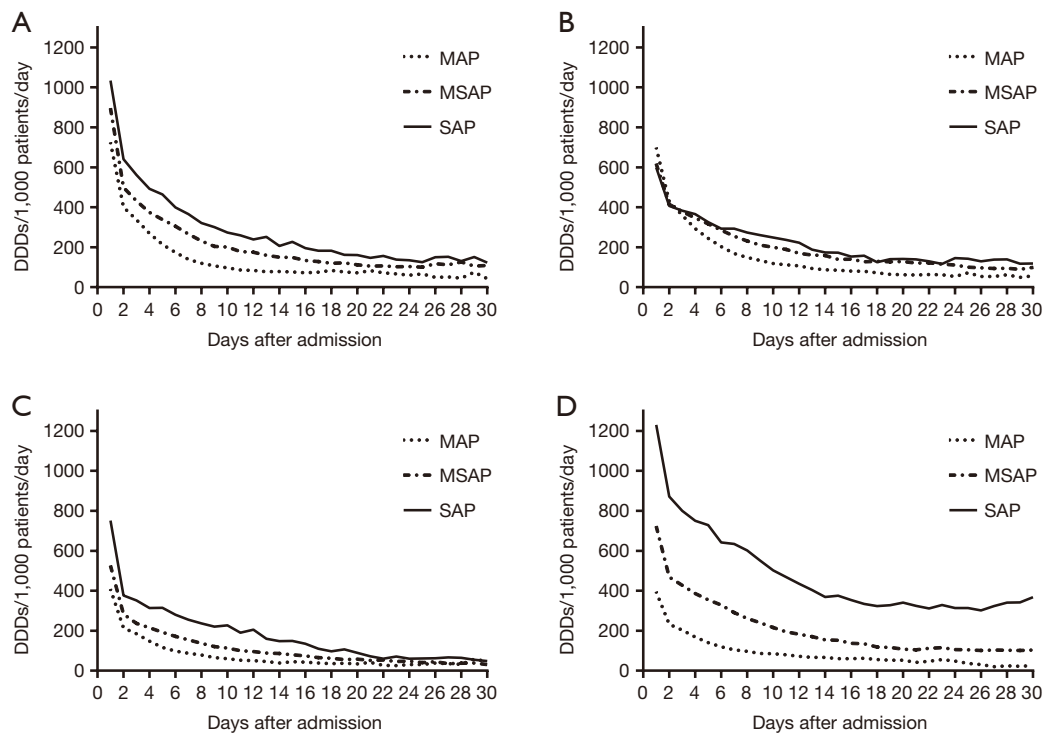


Figure 4 Daily prescription of trypsin inhibitor medications from the first day following admission to the 30th day. (A) Somatostatin; (B) octreotide; (C) gabexate; (D) ulinastatin. DDD, defined daily dose.

hospital mortality, some critically ill or fulminant patients may have died before diagnosis and some may have been prematurely discharged after resuscitation failure, which are common scenarios in China. After patients were classified as MAP, MSAP, or SAP, we found that age and chronic comorbidities were associated with disease severity and the relationship between gender and disease severity was not significant, aligning with the current consensus.

Use of TSI during AP treatment

This real-world study revealed that overall, SSTAs and TSIs are mainstay treatment measures for AP treatment in China; this is despite their unpopular status in the treatment guidelines of the US and Europe (14,15). Chinese physicians prescribe one or more TSIs for more than 90% of AP patients, and treatment with these drugs usually begin immediately after admission. The 48-h period after admission is crucial for AP treatment as patients tend to develop systemic inflammatory response syndrome, organ failure, and other systemic complications during this period. Treatment with SSTAs and TSIs usually lasts 1 week. As

the Revised Atlanta Classification for Acute Pancreatitis defines the first week of AP as the early phase (5), the above drugs tend to be used in the early phase of AP. For the early phase of AP, physicians tend to use somatostatin and octreotide and large doses of ulinastatin tend to be given to patients, particularly SAP patients. This is because some published papers showed that SSTAs and ulinastatin are beneficial for patients with AP (16-18). For drug combinations, combining SSTAs and ulinastatin appears as a routine combination used by physicians. However, when disease is mild, SSTA monotherapy is more widely used. This finding might be because SSTAs can inhibit pancreatic secretion, while ulinastatin inhibits interleukin and other inflammatory factors. Together, they exhibit pharmacological synergy and are thus frequently used.

From January 2015 to June 2017, overall prescription volume and patient utilization rate for the patients were stable, indicating that the usage of these drugs was less affected. Significant fluctuations in drug consumption and utilization rate were found when these drugs were used in SAP patients; however, this may be due to the low number of patients used in the study. A significant difference was

found in the usage of somatostatin and ulinastatin based on disease severity. To add, this drug combination may be an easy option for SAP patients. As drug consumption was found to trend after patients were admitted, this further validated the use of these drugs at the early stage of the disease.

Interestingly, we found that in addition to a large increase in the consumption of ulinastatin after disease worsening, a high prescription volume of ulinastatin remains at the later stages of disease progression [1 week after admission; studies have shown that persistent organ failure is the key determinant of mortality in AP, which aggravates the occurrence and progression of multiple organ dysfunction syndrome. Persistent resulted in a mortality of 25% compared to 8% with transient systemic inflammatory response syndrome (19,20)]. The most common cause of death 2 weeks after AP onset is usually sepsis and its complications (21,22). Studies have proven that the use of ulinastatin in SAP patients can significantly reduce the incidence and mortality rate of new organ failure (9,23). As a trypsin inhibitor, in addition to effectively inhibiting inappropriately-activated trypsin, ulinastatin can also effectively inhibit the secretion of many inflammatory factors and lysosomes. Ulinastatin can bind to calcium ions to inhibit the influx of calcium ions and block the TNF- α signaling pathway. Ulinastatin can also stabilize the cell membrane and lysosomal membrane to effectively inhibit the release of many hydrolases in lysosomes to block the inflammatory cascade and reduce cell damage (24-27). Studies have also proven that ulinastatin can effectively decrease the 28-day all-cause mortality of severe sepsis and septic shock, reduce the incidence of new multiple organ dysfunction syndrome, and shorten the length of hospitalization (28). These real-world clinical results prove that enzyme inhibition and anti-inflammatory drugs are important therapeutic measures based on the pathophysiological changes of AP (29-31). In SAP treatment, sufficient dose and duration of ulinastatin can benefit patients.

Study strengths and limitations

Real-world studies serve as current drug research hotspots; however, they exist in the preliminary exploratory stage in China. The incidence of AP is less than 1/1,000 and requires a large population to obtain large-scale results. The statistical data obtained from this study can however supplement this research domain. The present study had

major limitations. Similar to other retrospective database studies, there were errors and omissions during the retrieval of patient diagnosis or comorbidity data based on the ICD-10th diagnosis code. To add, we could not review patients because of the characteristics of the database itself. When patients were being stratified, complete matching with the classification criteria presented in the guidelines was not achieved as some SAP patients were classified as MSAP patients. Lastly, the dose used to treat AP was selected by default. Octreotide and other drugs may be used for gastric varices, which will result in errors when calculating dosing.

Conclusions

In summary, SSTAs and TSIs are the major therapeutic drugs for AP treatment and are widely utilized in China at the early stage of the disease, with a treatment cycle lasting 1 week. Although somatostatin and octreotide are the most commonly-used drugs, ulinastatin is widely used for SAP and the late stage of AP.

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Footnote

Reporting Checklist: The authors have completed the STROBE Reporting Checklist. Available at <http://dx.doi.org/10.21037/apm-19-363>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/apm-19-363>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-19-363>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The clinical research ethics boards of the Changhai Hospital waived the needs for participants' informed consent because the study was retrospective, anonymous, and non-interventional. All

methods in this study were performed in accordance with the relevant regulations and guidelines and the patients' personal data had been well protected. The review and approval of this study was exempted by the ethics committee of Changhai Hospital.

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