AstraZeneca

STUDY REPORT SYNOPSIS (ABSTRACT)

China Survey of Proton Pump Inhibitor Empirical Treatment in Management of Outpatients with Gastroesophageal Reflux Disease

Background/Rationale:

PPI (proton pump inhibitor) empirical treatment for gastroesophageal reflux disease (GERD) is recommended in recent Chinese GERD consensus which was published in October, 2014. It can help improving the symptoms, and also can help diagnosing GERD, which lacks single perfect test for establishing the diagnosis.

In China, it's been reported 13.6% GI (gastrointestinal) outpatients suffer from GERD typical symptoms but only 36.9% of them will have endoscopy. For the rest of 63.1% GERD patients, PPI can be used as empirical treatment for symptom improvement and further diagnosis.

Foreign clinical data shows 86.4% of GERD patients considered responders to treatment after 4 weeks of treatment with esomeprazole but there is no real-world data showing the efficacy of short-term PPIs empirical treatment in China.

Objectives

Primary Objective

To estimate the overall responder rate after 4 weeks of PPIs empirical treatment in patients with typical symptoms of GERD.

Main Secondary Objectives

Secondary objectives of the NIS are

- To estimate the overall responder rate after 2 weeks of PPIs empirical treatment.
- To estimate the proportion of patients in each Gerd Q cut-off range at each visit.
- To estimate responder rate respectively after 2 and 4 weeks of different PPIs empirical treatment.

- To estimate the onset of time of the response.

Table S1 Study objective and variable

objective	Outcome variable	Type
Primary To estimate the overall responder rate after 4 weeks of PPIs empirical treatment in patients with typical symptoms of GERD.	**Primary** The overall responder rate after 4 weeks of PPIs empirical treatment. Responder is defined as heartburn/ regurgitation frequency ≤1 days during 7 days before evaluation visit, assessed using Gerd Q questionnaire at each post-baseline visit.	Statistical analysis
Secondary 1) To estimate the overall responder rate after 2 weeks of PPIs empirical treatment; 2) To estimate the proportion of patients in each Gerd Q cut-off range at each visit; 3) To estimate responder rate respectively after 2 and 4 weeks of different PPIs empirical treatment; 4) To estimate the onset of time of the response.	**Secondary** 1) The overall responder rate after 2 weeks of PPIs empirical treatment; 2) The proportion of patients in each Gerd Q cut-off range at 2nd and 3rd visit (Gerd Q range: ≤2; 3-7; 8-10; 11-18); 3) The responder rate respectively after 2 and 4 weeks of different PPIs empirical treatment; 4) The median time to response (heartburn/ regurgitation frequency ≤1 days during last 7 days assessed using patient's dairy card) overall and for different PPIs, respectively.	Statistical analysis

Methods

Study Design

It's a multicentre, prospective, observational study.

Subject Population

The subject population included in the NIS were the consecutive outpatients between 18 and 65 years old with Gerd Q≥8 and without endoscopy examination plan within 4 weeks, while the gastroenterologists already prescribed PPI as empirical treatment.

During this study, 1000subjects in outpatient clinic of Gastroenterology departments were enrolled and 987 subjects were included in FAS according to the data integrity.

Statistical Methods

Statistical methods were primarily descriptive in nature.

For continuous data, descriptive statistics were presented as number of patients (n), mean, standard deviation (SD), median, minimum and maximum. For categorical data, the frequency and percentage of patients in each category were presented. Counts that are zero were displayed as "0". Percentages were based on non-missing data unless otherwise specified. The median of time to response were estimated using Kaplan-Meier method.

Results

Primary Objective

The primary objective of this NIS was to estimate the overall responder rate after 4 weeks of PPIs empirical treatment. Among 987 patients included in FAS, there were a total of 818 patients had the efficacy evaluation data being collected after PPIs treatment, and there were 582 responders among 818 patients, the responder rate was 71.1% (95% CI 67.9%-74.2%). For the patients who had the efficacy evaluation data being collected for less than 4 weeks, the response conditions of 4 weeks of PPIs empirical treatment were assess based on the last 7 days of symptoms. There were a total of 739 patients who completed 4 weeks of PPIs empirical treatment and had the efficacy evaluation data of 4 weeks, of which 534 patients got response, the responder rate was 72.3% (95% CI 68.9%-75.5%). Among 707 patients included in PPS, there were 513 responders who completed 4 weeks of PPIs empirical treatment, the responder rate was 72.6% (95% CI 69.1%-75.8%).

Secondary Objectives

For the patients who had the efficacy evaluation data being collected for less than 2 or 4 weeks, the response conditions of 2 or 4 weeks of PPIs empirical treatment were assess based on the last 7 days of symptoms. In the following text, in addition to the responded patients who completed PPIs empirical treatment as per protocol, the patients who withdrew prematurely and got responded based on the last 7 days of symptoms were taken into the calculation as the responders.

1) **The overall responder rate after 2 weeks of PPIs empirical treatment**

Among 987 patients included in FAS, there were 466 responders among 818 patients who had the efficacy evaluation data being collected after PPIs treatment at week 2; the overall responder rate was 57.0% (95% CI 53.5%-60.4%).

2) The proportion of patients in each Gerd Q cut-off range at each visit

At baseline visit, 56.9% (562/987) had the Gerd Q score of 8-10, and 43.1% (425/987) had the Gerd Q score of 11-18; the mean Gerd Q values was 10.5±1.92. The Gerd Q scores of patients decreased gradually with the duration of PPI treatment. After 2 weeks of empirical treatment, the proportion of patients with less than 8 of Gerd Q score reached to 64.4%, which including 1.2% (10/818) patients with Gerd Q score of ≤2 and 63.2% (517/818) those with the score of 3-7, and the mean Gerd Q score decreased to 6.9±2.27, which was 3.6±2.82 lower than baseline. Then after 4 weeks of empirical treatment, the proportion of patients with less than 8 of Gerd Q score reached to76.7%, which including 0.5% (4/739) patients with Gerd Q score of ≤2 and 76.2% (563/739) those with the score of 3-7; the mean Gerd Q value decreased to 6.6±1.80, which was 3.9±2.49 lower than baseline.

3) **Responder rate with different PPIs after 2 and 4 weeks of empirical treatment**

There were 6 kinds of PPIs used as empirical treatment for GERD in this study, including esomeprazole (57.1%, 564/987), rabeprazole (20.4%, 201/987), lansoprazole (11.3%, 112/987), pantoprazole (10.7%, 106/987), omeprazole (7.7%, 76/987) and ilaprazole (0.1%, 1/987). On the whole, compared with 2 weeks of empirical treatment, the responder rates of 4 weeks of different PPIs empirical treatment in GERD outpatients were increased. Detailed data could be found below.

The responder rates of patients with esomeprazole or with other PPIs were summarized. The responder rate after 2 and 4 weeks of esomeprazole was 57.1% (268/469) (95%CI 52.5%-61.7%) and 72.9% (342/469) (95% CI 68.7%-76.9%), respectively; while the responder rate after 2 and 4 weeks of other PPIs was 56.7% (198/349) (95% CI 51.4%-62.0%) and 68.8% (240/349) (95% CI 63.6%-73.6%), respectively.

The responder rates of patients with other PPIs than esomeprazole were further summarized individually. After 2 weeks of empirical treatment, the responder rate of patients used

lansoprazole was 72.0% (54/75) (95% CI 60.4%-81.8%); it was 61.7% (37/60) (95% CI 48.2%-73.9%) for patients with omeprazole, 52.7% (39/74) (95% CI 40.7%, 64.4%) for patients with pantoprazole, and 48.6% (68/140) (95% CI 40.0%-57.2%) for patients with rabeprazole. After 4 weeks of empirical treatment, the responder rates of patients used lansoprazole, omeprazole, pantoprazole or rabeprazole were 77.3% (58/75) (95% CI 66.2%-86.2%), 73.3% (44/60) (95% CI 60.3%-83.9%), 71.6% (53/74) (95% CI 59.9%-81.5%), and 60.7% (85/140) (95% CI 52.1%-68.9%), respectively.

The distribution of patients in each Gerd Q cut-off range at baseline was different among patients with different PPIs, implying that the distribution of disease severity might be imbalanced across different PPIs when the PPIs were prescribed initially. Higher Gerd Q score indicates a higher level of the symptoms severity and/or the turbulence of the disease to patients' quality of life. To demonstrate the disease severity distribution of patients at baseline, the baseline Gerd Q score was dichotomized into 2 levels using the cut-off of 8-10 and 11-18 and a summary for the patients' distribution on the dichotomized baseline Gerd Q levels for different PPIs was generated based on it. The percentage of patients with the lower Gerd Q cut-off range of 8-10 at baseline in lansoprazole were higher than other PPIs, while the percentage of patients with the higher Gerd Q cut-off range of 11-18 at baseline in omeprazole were higher than other PPIs. This imbalance might have impact to the responder rate to some extent. Therefore, the responder rate of patients with different PPI empirical treatment was also analysed on different baseline Gerd Q levels. In patients with esomeprazole, the responder rate was 72.9% (191/262) (95% CI 67.1%-78.2%) in those with baseline Gerd Q scale score of 8-10, and 72.9% (151/207) (95% CI 66.4%-78.9%) in those with baseline Gerd Q scale score of 11-18 after 4 weeks of empirical treatment; the responder rates in patients with pantoprazole were 71.4% (30/42) and 71.9% (23/32)respectively in different baseline Gerd Q cut-off range groups; the responder rates in patients with lansoprazole were 80.7% (46/57) and 66.7% (12/18) respectively; the responder rates in patients with omeprazole were 73.1% (19/26) and 73.5% (25/34) respectively, the responder rates in patients with rabeprazole were 58.7% (44/75) and 63.1% (41/65)respectively. In addition, assuming the number of patients with a baseline Gerd Q value of 8-10 was equal to the number of those with a value of 11-18, the weighted responder rate was 72.9% in patients

with esomeprazole, 71.7% in those with pantoprazole, 73.7% in those with lansoprazole, 73.3% in those with omeprazole, and 60.9% in those with rabeprazole at week 4.

4) **The onset of time to the response**

The overall median time to response from PPI empirical treatment was 13 days. The median times to response for esomeprazole and other PPIs empirical treatment were 12 days and 14 days, respectively.

Safety Results

Due to the non-interventional character of this study and since there is no requirement for the patients to use an AstraZeneca drug, no pro-active safety data collection was performed per protocol. Only spontaneously mentioned safety events were reported and no analysis was planned.

Conclusions

1. The responder rates after 4 weeks of PPIs empirical treatment in FAS and in PPS were 72.3% (534/739) and 72.6% (513/707) respectively among patients who completed 4 weeks of PPIs treatment; and the responder rate was 71.1% (582/818) among subjects who had the efficacy evaluation data being collected after PPIs treatment in FAS.

2. The responder rates after 2 weeks of PPIs empirical treatment were 57.0% (466/818) among patients who had the efficacy evaluation data being collected after PPIs treatment in FAS.

3. The GERD patients obtained symptom-relief (Gerd Q values of <8) over the duration of PPIs empirical treatment.

4. There were 6 kinds of PPIs used as empirical treatment for GERD in this study, including esomeprazole, rabeprazole, lansoprazole, pantoprazole, omeprazole and ilaprazole.

5. The responder rate after 2 and 4 weeks of esomeprazole was 57.1% (268/469) and 72.9% (342/469) respectively; while the responder rate after 2 and 4 weeks of other PPIs was 56.7% (198/349) and 68.8% (240/349) respectively.

6. On the whole, the responder rate of 4-week PPIs empirical treatment was higher than that of 2-week.

7. The overall median time to response after PPI empirical treatment was 13 days. The median times to response for esomeprazole and other PPIs empirical treatment were 12 days and 14 days, respectively.