

Point-by-point response to the editor:

**q1: Regarding the statistical statement:**

As mentioned by the editor, we described the statistical statement and provided it in PDF format.

Added sentence

Revised (Page 4 Line 2):

**Biostatistics statement:** The statistical methods of this study were reviewed by Ryuta Takenaka from Tsuyama Chuo Hospital.

Revised (Page 10 Line 19):

The statistical methods of this study were reviewed by Ryuta Takenaka from Tsuyama Chuo Hospital.

**q2: Regarding the files about the statement:**

As suggested by the editor, I provided them in a PDF format.

**q3: Regarding the COMMENTS:**

As suggested by the editor, I wrote the COMMENTS section.

Inserted sentence

Revised (Page 14 Line 9):

**COMMENTS**

*Background*

Proton pump inhibitors (PPIs) are considered to be more cost-effective for patients with GERD than first-generation histamine receptor-2 antagonists (H2RAs). Lafutidine is a second-generation H2RA that has a potent and sustained anti-acid secretory effect. In LAFORE trials conducted in Japanese patients with mild GERD, lafutidine was superior to first-generation H2RA (famotidine). The aim of this study was to compare the clinical efficacy of lafutidine with that of PPI (lansoprazole) as initial and maintenance treatment in Japanese patients with mild GERD.

### *Research frontiers*

GERD is a chronic disorder and long-term acid-suppression therapy is necessary in most cases. Limitations of PPIs include a higher cost than H2RAs, and potential side effects related to hypochlorhydria and hypergastrinemia.

### *Innovations and breakthroughs*

Lansoprazole was superior to lafutidine in Japanese patients with mild GERD, not only with respect to lowering the severity of heartburn, but also the satisfaction score. The hypothesis that lafutidine had similar efficacy and superior cost-effectiveness compared with lansoprazole in Japanese patients with mild GERD was not confirmed.

### *Applications*

The efficacy of a second-generation H2RA over a PPI in Japanese patients with mild GERD was not demonstrated, most notably during maintenance therapy.

### *Terminology*

Lafutidine is a second-generation H2RA and shown to be superior to first-generation H2RA (famotidine).

### *Peer-review*

#### **q4: Regarding the references**

As the editor pointed out, we corrected the PubMed citation numbers, DOI citation and the list of authors.

#### **References**

1. **Vakil N**, van Zanten SV, Kahrilas P, **Dent J**, **Jones R**. The Montreal definition

and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006; **101**:1900–1920 [PMID: 16928254]

2. **Khan M**, Santana J, Donnellan C, **Preston C**, **Moayyedi P**. Medical treatments in the short term management of reflux oesophagitis. *Cochrane database Syst Rev*. 2007; **2**:CD003244 [PMID: 17443524]
3. **Moayyedi P**, Talley NJ. Gastro-oesophageal reflux disease. *Lancet*. 2006; **367**:2086–2100 [PMID: 16798392]
4. **Sato H**, Kawashima K, Yuki M, **Kazumori H**, **Rumi MA**, **Ortega-Cava CF**, **Ishihara S**, **Kinoshita Y**. Lafutidine, a novel histamine H<sub>2</sub>-receptor antagonist, increases serum calcitonin gene-related peptide in rats after water immersion-restraint stress. *J Lab Clin Med*. 2003; **141**:102-105 [PMID: 12577045]
5. **Nakano M**, Ajioka H, Abe M, **Kiniwa M**. Possible involvement of host defense mechanism in the suppression of rat acute reflux esophagitis by the particular histamine H<sub>2</sub> receptor antagonist lafutidine. *Pharmacology*. 2012; **90**:205-211 [PMID: 23038658 DOI: 10.1159/000342386]
6. **Ohara S**, Haruma K, Kinoshita Y, **Kusano M**. A double-blind, controlled study comparing lafutidine with placebo and famotidine in Japanese patients with mild reflux esophagitis. *J Gastroenterol*. 2010; **45**:1219-1227 [PMID: 20632193 DOI: 10.1007/s00535-010-0283-8]
7. **Kinoshita Y**, Adachi K, Fujishiro H. Therapeutic approaches to reflux disease, focusing on acid secretion. *J Gastroenterol*. 2003; **38** Suppl 15:13-19 [PMID: 12698865]

8. **Sigterman KE**, van Pinxteren B, Bonis PA, **Lau J**, **Numans ME**. Short-term treatment with proton pump inhibitors, H<sub>2</sub>-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev*. 2013; **5**:CD002095 [PMID: 23728637 DOI : 10.1002/14651858]
9. **Dial S**, Delaney JA, Barkun AN, **Suissa S**. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA*. 2005; **294**:2989-2995 [PMID: 16414946]
10. **Aseeri M**, Schroeder T, Kramer J, **Zackula R**. Gastric acid suppression by proton pump inhibitors as a risk factor for *clostridium difficile*-associated diarrhea in hospitalized patients. *Am J Gastroenterol*. 2008; **103**:2308-2313 [PMID: 18702653 DOI: 10.1111/j.1572-0241.2008.01975.x]
11. **Howell MD**, Novack V, Grgurich P, **Soulliard D**, **Novack L**, **Pencina M**, **Talmer D**. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med*. 2010; **170**:784-790 [PMID: 20458086 DOI: 10.1001/archinternmed.2010.89]
12. **Hess MW**, Hoenderop JG, Bindels RJ, **Drenth JP**. Systematic review: hypomagnesaemia induced by proton pump inhibition. *Aliment Pharmacol Ther*. 2012; **36**:405-413 [PMID: 22762246 DOI: 10.1111/j.1365-2036.2012.05201.x]
13. **Recker RR**. Calcium absorption and achlorhydria. *N Engl J Med*. 1985; **313**:70-73 [PMID: 4000241]
14. **Yu EW**, Bauer SR, Bain PA, **Bauer DC**. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med*. 2011;

**124**:519-526 [PMID: 21605729 DOI: 10.1016/ j.amjmed.2011.01.007]

15. **Komazawa Y**, Adachi K, Mihara T, **Mihara T**, **Ono M**, **Yuki M**, **Kawamura A**, **Karim Rumi MA**, **Amano Y**, **Kinoshita Y**. Tolerance to famotidine and ranitidine treatment after 14 days of administration in healthy subjects without *Helicobacter pylori* infection. J Gastroenterol Hepatol. 2003; **18**:678-682 [PMID: 12753150]