CONFLICT OF INTEREST

Y.K. received honoraria from AstraZeneca K.K., Daiichi-Sankyo Co., Ltd., and Takeda Pharmaceutical Co., Ltd.

REFERENCES

1. Molina-Infante J, Rodriguez-Sanchez J, Martinek J *et al.* Long-term loss of response in proton pump inhibitor-responsive esophageal eosinophilia is uncommon and influenced by CYP2C19 genotype and rhinoconjunctivitis. Am J Gastroenterol 2015;110:1567–75.
2. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:13–22.
3. Sakurai Y, Mori Y, Okamoto H *et al.* Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects--a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42:719–30.
4. Sakurai Y, Nishimura A, Kennedy G *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Japanese subjects. Clin Transl Gastroenterol 2015;6:e94.
5. Hunt RH, Scarpignato C. Potassium-competitive acid blockers (P-CABs): are they finally ready for prime time in acid-related disease? Clin Transl Gastroenterol 2015;6:e119.
6. Cheng E, Zhang X, Huo X *et al.* Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut 2013;62:824–32.

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Response to Ishimura *et al.*

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To the Editor: We read with great interest the comments of Ishimura *et al.* (1) on our study evaluating the influence of CYP2C19 genotype on the long-term effectiveness of proton pump inhibitor (PPI) therapy in patients with PPI-responsive esophageal eosinophilia (PPI-REE) (2). As foretold in a recent international position paper on PPI-REE (3), it will be important to eventually determine if patients with PPI-REE would also respond to other classes of anti-acid drugs, as it would be informative of acid-induced damage as a primary driver for the disease. In the letter by Ishimura *et al.* (1), the authors present for the first time four patients with symptomatic esophageal eosinophilia unresponsive to esomeprazole 20 mg/day for 12 weeks, three of whom eventually achieved clinical and histological remission on vonoprazan 20 mg/day for 12 weeks (1). Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) recently approved in Japan that, compared to esomeprazole, has shown more potent and sustained acid suppression and less impairment by CYP2C19 polymorphisms (4).

We would like to reflect on some potential flaws of this series:

1. PPI doses for inducing eosinophilic esophagitis (EoE) remission were low (esomeprazole 20 mg/daily). Consequently, responsiveness to PPI therapy might have been underestimated. All available guidelines on EoE recommend an initial trial of PPI therapy consisting of omeprazole or its equivalent 20–40 mg twice daily (5,6). A trend towards increased efficacy for PPIs when administered twice daily compared with once daily has been shown in a recent meta-analysis (7). Compared to esomeprazole 20 mg/daily, vonoprazan 20 mg/daily achieves significantly longer periods with gastric pH>4 (95% vs. 68%) (4). A fairer comparison would have been starting with esomeprazol 20–40 mg twice a day and then reevaluating the efficacy of vonoprazan in non-responders to PPI therapy, or, even better, a randomized crossover controlled trial comparing esomeprazole and vonoprazan.
2. Three patients in this series responded to vonoprazan, but this does not prove that acid suppression was the one and only mechanism involved. Likewise, the reason why one patient did not respond needs to be clarified. The role of the potassium channel encoded by KCNJ2, the only gene that has exhibited a differential expression in EoE patients (responders and non-responders) to PPI therapy (8), should be further explored.
3. A CYP2C19 rapid metabolizer genotype may hamper the long-term efficacy of tapering PPI doses in PPI-REE (2). However, no study has assessed the influence of CYP2C19 polymorphisms in initial EoE remission, neither with PPIs nor with P-CABs. If the existence of P-CAB-responsive EoE is confirmed, vonoprazan would show a clear advantage for long-term management advantage in Western populations, in which up to 70% of patients may show a CYP2C19 rapid metabolizer genotype (2).
4. The ultimate mechanisms by which PPI therapy accomplishes its effects on esophageal eosinophilia remain unclear yet (3). Aside from acid suppression, the anti-inflammatory effects of PPI therapy have been proven in a murine model of asthma (9) and EoE cell cultures (10).

We would like to sincerely congratulate Ishimura *et al.* for this interesting series, which adds even more controversy to this fascinating and challenging, but somewhat confusing, entity, so-called PPI-REE. As for EoE, further studies should compare head-to-head PPIs and P-CABs at equivalent dosage, evaluate the influence of CYP2C19 and KCNJ2 polymorphisms in remission rates for both drugs, and rule out the existence of potential anti-inflammatory effects for vonoprazan, irrespective of acid suppression.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Ishimura N, Ishihara S, Kinoshita Y. Sustained acid suppression by potassium-competitive acid blocker (P-CAB) may be an attractive treatment candidate for patients with eosinophilic esophagitis. Am J Gastroenterol 2016;111:1203–4 (this issue).

7. Molina-Infante J, Rodriguez-Sanchez J, Martinek J *et al.* Long-term loss of response in proton pump inhibitor-responsive esophageal eosinophilia is uncommon and influenced by CYP2C19 genotype and rhinoconjunctivitis. Am J Gastroenterol 2015;110:1567–75.
8. Molina-Infante J, Bredenoord AJ, Cheng E *et al.* Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut 2016;65:524–31.
9. Kagami T, Sahara S, Ichikawa H *et al.* Potent acid inhibition by vonoprazan in comparison with esomeprazole with reference to CYP2C19 genotype. Aliment Pharmacol Ther 2016;43:1048–59.
10. Liacouras CA, Furuta GT, Hirano I *et al.* Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allerg Clin Immunol 2011;128:3–10.
11. Dellon ES, Gonsalves N, Hirano I *et al.* ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679–92.
12. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histological remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:13–22.e1.
13. Wen T, Dellon ES, Moawad FJ *et al.* Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. J Allergy Clin Immunol 2015;135:187–97.
14. Cortes JR, Rivas MD, Molina-Infante J *et al.* Omeprazole inhibits IL-4 and IL-13 signaling signal transducer and activator of transcription 6 activation and reduces lung inflammation in murine asthma. J Allergy Clin Immunol 2009;124:607–10.
15. Cheng E, Zhang X, Huo X *et al.* Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut 2013;62:824–32.

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Bulb Biopsy in Adult Celiac Disease: Pros Outweigh the Cons?

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To the Editor: We read the excellent study by the Taavela *et al.* (1) suggesting caution when considering the diagnosis of pediatric celiac disease based on a duodenal bulb biopsy. We completely agree and share their concerns. However, we would like to pose a question: what are the "big issues" in adult celiac disease? We would suggest that they are delays in diagnosis and under-diagnosis. Both US and UK studies have revealed that 5–13.6% of patients with newly diagnosed celiac disease have had a prior endoscopy where a chance to diagnose celiac disease was missed (2,3). By advocating a bulb biopsy, the diagnostic rate is increased by ~10% (**Table 1**). Caution is required in the selection of patients who should have this performed—weight loss, anemia, diarrhea, family history, or positive serology; however, for routine practice, a duodenal bulb biopsy may not be necessary. The Finnish group has shown that all their cases of celiac disease had TG-2 IgA deposits within the bulb biopsy, which we believe further supports the merit of a bulb biopsy (1). We have historically reported that 100% sensitivity for the detection of celiac disease can only be achieved in the presence of a

Table 1. Studies evaluating the diagnostic yield of taking duodenal bulb biopsies

Year	Authors	Country	Adults/pediatrics	Number of patients	Number of celiac disease (%)	Number of USCD (%)
2001	Vogelsang *et al.* (6)	Austria	Adults	51	21 (41.2%)	2 (9.5%)
2004	Bonamico *et al.* (7)	Italy	Pediatrics	95	95 (100%)	4 (4.2%)
2005	Brocchi *et al.* (8)	Italy	Adults	1	1 (100%)	1 (100%)
2008	Hopper *et al.* (4)	UK	Adults	56	56 (100%)	1 (1.8%)
2008	Bonamico *et al.* (9)	Italy	Pediatrics	1013	665 (65.6%)	16 (2.4%)
2009	Rashid *et al.* (10)	Canada	Pediatrics	35	29 (81.6%)	3 (11.4%)
2010	Weir *et al.* (11)	USA	Pediatrics	198	198 (100%)	10 (5.1%)
2010	Mangiavillano *et al.* (12)	Italy	Pediatrics	47	42 (89.4%)	5 (11.9%)
2010	Gonzalez *et al.* (13)	USA	Adults	80	40 (50%)	5 (12.5%)
2011	Levinson-Castiel *et al.* (14)	Israel	Pediatrics	87	87 (100%)	6 (7.0%)
2011	Evans *et al.* (5)	UK	Adults	376	126 (33.5%)	11 (9.0%)
2012	Kurien *et al.* (5)	UK	Adults	77	28 (36.4%)	5 (17.9%)
2013	Sharma *et al.* (15)	Australia	Pediatrics	101	101 (100%)	8 (7.9%)
2014	Caruso *et al.* (16)	Italy	Adults	42	25 (59.5%)	0 (0%)
2016	Stoven *et al.* (17)	USA	Adults	679	16 (2.4%)	1 (6.2%)

USCD, ultra-short celiac disease.