Eosinophilic esophagitis that develops during therapy with proton pump inhibitors : case series and possible mechanisms

Rok Orel[1], Simon Murch[2], Jorge Amil Dias[3], Yvan Vandenplas[4], Matjaž Homan[1]

(1) Department of Gastroenterology, Hepatology and Nutrition, University Children's Hospital Ljubljana ; Faculty of Medicine, University of Ljubljana, Slovenia ; (2) University Hospital Coventry & Warwickshire, UK ; (3) Centro Hospitalar S. João, Porto, Portugal ; (4) Vrije Universiteit Brussel, Brussels, Belgium.

Abstract

Therapy with proton-pump inhibitors (PPIs) results in remission in at least one third of patients with esophageal eosinophilia, presumably because of both their acid-related and anti-inflammatory mechanisms of action. However, eosinophilic esophagitis (EoE) may also develop during therapy with PPIs. We present a case series of four children who were initially diagnosed with infectious esophagitis, gastroesophageal reflux disease or gastric ulcer, who had no eosinophilic infiltration of the esophagus, but subsequently developed symptoms, endoscopic features and histological picture of typical EoE. We discuss mechanisms of action of PPIs of likely relevance to an increased risk of development of EoE in some patients , such as their influence on mucosal barrier function, interference with pH-related protein digestion by pepsin, and antigen processing by immune cells. (Acta gastroenterol. belg., **2016**, 79, **245-250**).

Key words : esophageal eosinophilia, eosinophilic esophagitis, proton pump inhibitors, gastroesophageal reflux disease, digestion.

Introduction

Esophageal eosinophilia, the finding of eosinophilic granulocytes in the squamous epithelium of the esophagus, is abnormal, as in health the esophageal epithelium does not contain eosinophils. The current definition of esophageal eosinophilia relies on the presence of high number of eosinophils in the esophageal epithelium (1). Esophageal eosinophilia can be found in many different conditions, but three of them, eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD) and proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) are by far the most common.

EoE is a chronic, immune/antigen-mediated disease characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation, consisting of a peak value of ≥ 15 eosinophils per high-power field (1,2). Tissue eosinophilic infiltration should be limited to the esophagus and secondary causes of esophageal eosinophilia should be excluded. In addition, the diagnosis of EoE is confirmed only when esophageal eosinophilia does not resolve with treatment with high doses of PPIs lasting at least 8 weeks (1,2). According to published data, between 35% to 75% of patients who initially present with esophageal eosinophilia may achieve clinicopathologic remission on therapy with PPIs (3).

In some of these patients, classified as PPI-REE, the initial eosinophilia can be attributed to the underlying GERD. During peptic inflammation, presumably as a consequence of acid and pepsin induced damage to the esophageal epithelium, the epithelium becomes hyperplastic and accumulates eosinophils. In the 1980's and early 1990's the presence of intraepithelial esophageal eosinophils was regarded as pathognomonic for GERD (4,5), and early guidelines for diagnosis and treatment of EoE from 2007 recommended either 24-hour esophageal pH-metry or therapeutic trial with PPIs to discriminate the two diseases (6). However, as EoE and GERD may coexist or even increase the risk of each other (7), only unresponsiveness to PPIs has been regarded necessary for confirming the diagnosis of EoE in more recent guidelines (1,8).

Moreover, treatment with PPIs leads to a resolution of symptoms and esophageal eosinophilia in a substantial proportion of patients without GERD who do not having abnormal esophageal acid exposure. Although PPI responsiveness is significantly higher in patients with documented GERD compared to those without it (9), it cannot be predicted by the degree of pathological acid exposure measured by pH-metry (3). The phenotype of non-GERD PPI-REE is (with the exception of responsiveness to PPIs) practically indistinguishable to that of EoE unresponsive to PPIs, as both diseases were found to share similar symptoms, macroscopic changes observed during endoscopy, histology picture, gene expression and cytokine profile (3,10-14).

A number of mechanisms have been recognized in recent years that try to explain how PPIs may affect esophageal eosinophilia. As GERD itself can contribute to the development of esophageal eosinophilia, both through damaging the esophageal epithelial barrier possibly allowing penetration of allergens through the mucosa, and through cytokine mediated inflammation, at least a part of the effect of PPIs can be attributed to the inhibition of gastric acid secretion (15). Besides this, PPIs may possess direct anti-inflammatory effects. In vitro studies

Correspondence to : Rok Orel, M.D., Ph.D., University Children's Hospital Ljubljana, Faculty of Medicine, University of Ljubljana, Bohoričeva 20, 1000 Ljubljana, Slovenia. E-mail : rok.orel@kclj.si

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revealed that PPIs block Th2 cytokine-stimulated expression of eotaxin-3, the main chemo-attractant for eosinophils, in culture of esophageal epithelial cells taken from both GERD and EoE patients, presumably through blocking the signal transducer and activator of transcription (STAT) 6 signaling pathway (16,17). The transcriptome analysis in PPI-REE patients showed that PPIs down-regulate gene expression of Th2 cytokines and chemokines in these patients in similar manner to steroids in EoE patients (13,14).

While the aforementioned data suggest that PPI-REE may probably constitute a subphenotype of EoE rather than a separate disease entity (3), the reasons why some patients respond to PPI therapy and the others do not remain unclear. Moreover the published literature has practically overlooked the fact that some patients may even develop *de novo* EoE during a long-term treatment with PPIs for the indications other than esophageal eosinophilia. The aim of this paper is to report four such cases as well as to discuss the putative underlying mechanisms.

Case # 1

A 7-year old girl was admitted to the hospital with a five day history of severe chest pain, high fever, vomiting, and food refusal. Her family history was positive for asthma. Upper endoscopy showed profuse white exudates and massive erosions in the esophagus. Histological findings of multiple esophageal biopsies were consistent with infective esophagitis, with numerous neutrophils in the epithelium. No fungal elements were found. Focally, there were suspicious herpetic inclusions, but immunohistochemical reactions to HSV-1, HSV-2 and CMV were negative. A maximum 3 eos/HPF were detected in the epithelium. She received a 6-week course of PPI (20 mg/day) and had symptom remission in a few days. Four months later she presented with chest and upper abdominal pain. Treatment with PPIs was prescribed again. Because there was no improvement of symptoms in two months, a second endoscopy was performed, revealing longitudinal furrows in the esophagus. Histological examination demonstrated intense esophageal eosinophilic infiltration with up to 40 eos/HPF. The patient was tested for alimentary allergies with skin prick tests, patch tests and specific IgE determination, and the results revealed cow's milk protein allergy. An elimination diet devoid of cow's milk and dairy products was prescribed. After one month on a cow's milk-free diet, the intensity of her symptoms decreased. The number of eosinophils in the esophageal mucosa at the control endoscopy 2 months after introduction of diet was reduced, although not normal (9-12 eos/HPF). She continued to be on cow's milk elimination diet and was symptom free at follow-up.

Case # 2

An 11-year-old boy with spastic cerebral palsy was admitted to the hospital due to abdominal pain, food regurgitation, vomiting and cough that had been present for a few months. Upper endoscopy demonstrated erosive esophagitis (grade C of Los Angeles classification). No endoscopic features of EoE were present. Several biopsies from different parts of the esophagus revealed typical signs of reflux esophagitis but with only few eosinophils. He was given PPI (40 mg/day) and his gastrointestinal symptoms greatly diminished. After 13 months of constant therapy with PPI follow-up endoscopy was performed. The boy had little gastrointestinal symptoms considering his neurologic condition, but endoscopy showed longitudinal esophageal furrows. Histological changes demonstrated chronic esophagitis with dense eosinophilic infiltration of more than 50 eos/HPF. As there were no signs of reflux esophagitis the PPI dose was reduced (20 mg/day) and skin prick tests, patch tests and specific IgE determination for food allergies were performed. All the results were negative, even though the patient had positive personal and family history of respiratory allergies and asthma. The 6-food elimination diet (avoiding milk, egg, wheat, soy, nuts and see food) was proposed. However, elimination diet was not accepted by his parents, due to his neurological disorder which caused feeding difficulties as well as his paucity of symptoms. During several-years of follow-up his clinical condition has remained stable and the patient's parents have not agreed to control endoscopy.

Case # 3

A 9-year old boy was admitted to the hospital due to abdominal pain, nausea and vomiting. He was allergic to dust-mite and also had positive family history for allergies. Upper endoscopy showed low-grade erosive esophagitis and nodular antral gastritis. Histological findings confirmed *Helicobacter pylori* infection and reflux esophagitis without any eosinophil infiltration. He received triple therapy for *Helicobacter pylori* eradication and had rapid remission of symptoms. However, due to his recurrent reflux symptoms and former diagnosis of GERD he was treated with PPIs for several times in the following four-year period and eventually continuously for more than 6 months. Because of persistent symptoms upper endoscopy was performed and demonstrated longitudinal esophageal furrows, while biopsy results showed up to 10 eosinophils infiltrating the esophageal mucosa. Twenty-four-hour esophageal pH-monitoring confirmed pathologic acid reflux. Therefore, he was put on a long-term PPI therapy (40 mg/day). While on therapy with PPI for two months, he developed food impaction. Endoscopy showed longitudinal esophageal furrows with histologically proven dense eosinophilic infiltrate (over 60 eos/HPF). Complete allergology evaluation confirmed dust-mite allergy, but no sensitization to food allergens was found. The patient received 6-food elimination diet without symptomatic or histologic response. Therefore, swallowed budesonide 2 mg daily was prescribed. During several-years of follow-up the

boy was having continuing symptoms including several episodes of food impaction (but not esophageal stenosis) as well as profound esophageal eosinophilia at control endoscopies in spite of combined dietary/steroid treatment and PPI therapy for concomitant GERD.

Case # 4

A 7-month old boy was urgently admitted to the regional hospital because of hematemesis and melena that appeared during mild febrile upper respiratory tract infection. With the exception of mild anemia (Hb 90 g/l), all laboratory results were normal. He was immediately put on intravenous PPI 1mg/kg/12hours and transported to the university hospital, where upper endoscopy was performed within 24 hours from the beginning of symptoms of bleeding. A large prepyloric ulcer with diameter about 2 cm covered with fibrin clot was identified, while the mucosa of esophagus, stomach and duodenum appeared normal. The treatment with intravenous PPI 1 mg/kg/day continued for another three days and was thereafter switched to oral route. A control endoscopy 2 weeks later revealed partial but not complete healing of the ulcer and normal appearance of all other parts of upper gastrointestinal tract. Several biopsies were taken from the duodenum, stomach and lower third of the esophagus. Histology results were unremarkable including practically normal appearance of the esophageal mucosa without any eosinophilic infiltration. To speed up ulcer healing the dose of PPI was raised to 2 mg/kg/day. At discharge, the infant was completely symptom-free. Two months later, a control endoscopy was performed. While only a small scar was found at the place of former ulceration, discrete furrowing and white plaques were found in the esophagus. Multiple biopsies taken from different parts of the esophagus revealed typical signs of EoE with up to 40 eos/HPF in distal but normal histology picture in proximal parts of the esophagus. Complete allergy work-up including skin prick and patch tests and specific IgEs were negative. As the boy had no symptoms, no food allergen sensitization was found and family history for allergic disease was negative, parents refused any treatment for EoE but continued with PPI 1 mg/kg/day. At endoscopy 3 months later, longitudinal furrows of esophagus were more pronounced and histology confirmed progression of EoE with up to 88 eos/HPF in distal and 37 eos/HPF in proximal esophagus. Because the boy was still symptom-free, the only treatment accepted by the family was a therapeutic trial with cow's milk protein elimination diet. At control endoscopy following 4 months of the diet, the esophagus looked macroscopically normal. Consistent with this, histologic examination showed no residual signs of EoE, demonstrating almost complete disappearance of eosinophils from both proximal and distal esophagus. The boy continued on cow's milk elimination diet and remained symptom-free.

Discussion

Awareness that therapy with PPIs results in both symptomatic and histological remission in at least one third of patients with esophageal eosinophilia, together with growing knowledge about the dual acid-related and anti-inflammatory mechanisms of their action, has led to an assumption that PPIs may to a greater extent also prevent the development of EoE, especially in patients with underlying diseases that may increase the risk of this disorder. In contrast with that, Merwat and Spechler have suggested plausible mechanisms by which acid-suppressive medications may actually predispose to the development of EoE (18). We report four cases of patients who developed EoE while or soon after taking therapy with PPIs. Protective and putative harmful mechanisms of PPIs related to EoE development may be proposed.

From the mechanistically point of view, conditions that cause disruption of the esophageal epithelial barrier and increase its permeability to antigens may be regarded as potential factors that enhance the risk for EoE. Both infectious esophagitis (19,20), and caustic ingestion (21) have been proposed as potential causes of increased epithelial permeability that resulted in EoE. More importantly, one of the consequences of GERD is dilation of intercellular spaces (DIS) between esophageal epithelial cells, also termed "spongiosis", that may facilitate antigen penetration and exposure to antigen-recognizing cells (22,23). Several studies reported, although not uniformly, that a prevalence of GERD is considerably increased among EoE patients in comparison to general population (24-27), and that the prevalence of EoE may be high in patients after repair of esophageal atresia, a condition often associated with severe GERD (28,29). It has been shown that treatment with PPIs results in improvement of structural changes of the esophageal epithelium in both GERD (30) and PPI-REE (31). In this regard it is interesting that three of our cases with diseases affecting esophageal permeability, especially the two with erosive reflux esophagitis, did not develop EoE at the time of active disease but much later, when the disease was well controlled with medication.

One of the possible explanations is that the restoration of the epithelial integrity during therapy with PPIs may be incomplete or may not even occur, as observed in many patients with non-erosive reflux disease (NERD) who do not respond to PPIs (32). This would mean that, despite therapeutic efficacy of PPIs regarding symptom control and healing of the erosions, the epithelium might remain permeable for macromolecules in some patients. Even more controversial are the results of the study from Mullin *et al*. that compared mucosal permeability by sucrose permeability test before, during and after stopping treatment with esomeprazole in patients with GERD and healthy controls (33). Surprisingly they found that, in a few days after beginning therapy with PPI, mucosal permeability increased both in GERD patients and healthy volunteers, while it normalized in the latter only when

the treatment was stopped. This suggests that PPIs induce a significant transmucosal leak and compromise upper GI barrier function.

There is as yet no evidence that direct passage of triggering allergens through esophageal mucosal barrier and their local presentation to immune cells underlies the development of EoE. EoE is not a mucosa-restricted but a transmural disease of the esophagus, as demonstrated by endoscopic ultrasound and computed tomography studies as well as transmural sections in an EoE patient who underwent esophagectomy because of adenocarcinoma (34). The initial events contributing to eosinophil recruitment by stimulated T cells may well take place in the deeper layers of the esophagus (35). Therefore, the site of primary sensitization of the immune cells responsible for the development of Th2 driven immune response that results in EoE may be at sites distant from the esophagus, such as nasal-associated lymphoid tissue (NALT) in case of aeroallergens and gut-associated lymphoid tissue (GALT) in the case of food antigens (35).

Increase of gastric pH due to therapy with PPIs prevents activation of pepsinogens and the initiation of protein digestion in the stomach (36). That increases the possibility that, despite subsequent proteolysis by pancreatic and intestinal proteases and peptidases, some peptides remain big enough to serve as antigenic epitopes for intestinal immune cells and induce immune response. A group of scientists from Austria and Hungary published a series of papers demonstrating that highly digestible proteins such as codfish proteins remain undigested when pH was only marginally shifted from 2.5 to 2.75 (37). Ingestion experiments in healthy volunteers revealed absorption of biologically active undigested fish allergens only 10 minutes after ingestion, with maximal serum levels after 1 to 2 hours (38). In patients with known codfish allergy, skin prick testing with extract of experimental peptic digestion of fish proteins at pH 2 did not provoke skin reaction while extract digested at higher pH values did. When food challenge was performed in five of the patients with codfish allergy with predigested fish proteins, this revealed a 10- to 30-fold reduction of the tolerated cumulative antigen dose when the proteins had been digested under hypoacidic conditions. *In vivo*, the influence of acid-suppression on allergenicity of food proteins was tested in a BALB/c mice model (39,40). While feeding with caviar or hazelnut extract did not result in sensitization in untreated animals, mice taking acid-suppressive medications developed high titre food-specific IgE and IgG1 antibodies, T-cell reactivity and positive skin tests towards test allergens. Most importantly, the same group proved the relevance of these findings in humans by comparing markers of specific food sensitization, specific IgE formation and cytokine patterns, before and after 3 months of treatment with H2-blockers or PPIs in the cohort of 152 adult patients with negative history for atopy or allergy (36). Before treatment, 10% of patients had preexisting food-specific IgE antibodies to at least 1 of 19 tested food allergens, when after three months of treatment 26% of patients had positive specific IgEs. To exclude the influence of other environmental factors, such as a season of the year, they used a control group of 50 healthy subjects. The proportion of initially sensitized individuals with positive specific IgEs was similar to the experimental group but did not change until the end of the observation period. The calculated relative risk of development food sensitization after 3-months of anti-acid therapy was 10.5 (95% confidence interval : 1.44-76.48 ; p = 0,0203). In addition, before therapy total IgE levels in experimental and control group were similar, while they were significantly increased after 3 months of therapy in the first compared to the second. While the specific IgE levels normalized in majority of patients in the five months after the end of the therapy the percentage of patients with positive skin prick tests remained significantly higher than in control group.

The use of PPIs may induce increased intraepithelial infiltration with lymphocytes and inflammation in the lamina propria of the colon (41). A study retrospectively reviewed the medical records and histological reports of 78 patients receiving PPIs who had no symptoms of diarrhea, and their age- and gender- matched controls. The authors found a significantly higher intraepithelial lymphocyte count ($p < 0.001$) as well as the extent of the inflammation ($p < 0.001$) in the PPI group than in controls. These findings are quite unexpected with respect to known anti-inflammatory actions of PPIs and may represent a distal GI tract counterpart of EoE, antigen/immune-mediated inflammation.

In addition, there is the possibility that the increase in esophageal luminal pH induced by PPI therapy may directly affect eosinophil recruitment, because of the notable pH dependency of signaling through the CCR3 chemokine receptor. Indeed, an increase in pH from 7 to 7.6 causes a 10-fold increase in signaling, and would thus facilitate eosinophil recruitment through enhanced eotaxin-CCR3 response.

According to all aforementioned observations, use of PPIs, especially long-term, may significantly increase the risk of sensitization to common food antigens. The baby boy presented as our fourth case, for example, did not have any other risk factor except long lasting treatment with high doses of PPI when he developed EoE and cow's milk allergy. It is speculative to claim that PPI played a crucial role in this case. However, the influence of acid inhibition on protein digestion and immunogenicity may have additional implications. During reflux episodes the esophagus and in some instances the lymphatic tissues of pharynx (Waldeyer ring) can be exposed not only to acid and enzymes but also to food in stomach contents for much longer periods of time. Several studies using combined pH/impedance monitoring revealed that PPI therapy results only in significant reduction in esophageal acid exposure time but does not affect the total number of reflux episodes, the duration of esophageal bolus exposure and proximal extent of the reflux (42-6). PPIs may also delay gastric emptying of solids that may

additionally contribute to gastroesophageal reflux (47). It still remains to be explored whether the reflux and prolonged exposure of upper GI and respiratory tract to undigested food proteins is more harmful regarding their allergenic potential than to more digested ones.

Given that some patients show reduction in esophageal eosinophilia upon PPI therapy, while others show increase, it is likely that different mechanisms may modulate eosinophil recruitment in different patients. No evidence has however yet emerged for differential mucosal gene expression between these variants of EoE, and it thus remains possible that the effects of PPIs, for good or bad, may be mediated outside the esophagus itself in the inductive lymphoid tissues where primary sensitization takes place.

The principal limitation of our study is that we made conclusions on small study size- four children. Moreover, it is also possible that we somehow missed the EoE diagnosis in our group of patients at initial endoscopy, due to patchy distribution of the histological changes of the esophageal mucosa or seasonal variations of the esophageal eosinophilic inflammation.

In conclusion, anti-secretory and anti-inflammatory effects of PPIs may have relevant impact on EoE, and consequences of treatment with them may be potentially harmful in some patients. The awareness of this risk needs to be considered in planning future research on the pathogenesis, possible prevention and treatment of EoE and PPI-REE.

References

1. DELLON E.S., GONSALVES N., HIRANO I., FURUTA G.T., LIACOURAS C.A., KATZKA D.A. ACG clinical guideline : Evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. *Am. J. Gastroenterol*., 2013, **108** : 679-692.
2. PAPADOPOULOU A., KOLETZKO S., HEUSCHKEL R., DIAS J.A., ALLEN K.J., MURCH S.H. *et al*. Management guidelines of Eosinophilic management in Childhood. *J. Pediatr. Gastroenterol. Nutr*., 2014, **58** : 107-118.
3. MOLINA-INFANTE J., KATZKA D.A., DELLON E.S. Proton pump inhibitor-responsive esophageal eosinophilia : a historical perspective on a novel and evolving entity. *Rev. Esp. Enferm. Dig*., 2015, **107** : 29-36.
4. WINTERS H.S., MADERA J.L., STAFFORD R.J., GRAND R.J., QUINLAN J.E., GOLDMAN H. Intraepithelial eosinophils : a new diagnostic criterion for reflux esophagitis. *Gastroenterology*, 1982, **83** : 818-823.
5. BROWN J.F., GOLDMAN H., ANTONOLIO D.A. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. *Am. J. Surg. Pathol*., 1984, **8** : 899-905.
6. FURUTA G.T., LIACOURAS C.A., COLLINS M.H., GUPTA S.K., JUSTINICH C., PUTNAM P.E. *et al*. Eosinophilic esophagitis in children and adults : a systematic review and concensus recommendations for diagnosis and treatment. *Gastroenterology*, 2007, **133** : 1342-1363.
7. KATZKA D.A. The complex relationship between eosinophilic esophagitis and gastroesophageal reflux disease. *Dig. Dis*., 2014, **32** : 93-97.
8. LIACOURAS C.A., FURUTA G.T., HIRANO I., ATKINS D., ATTWOOD S.E., BONIS P.A. *et al*. Eosinophilic esophagitis : updated consensuc reccomendations for children and adults. *J. Allergy Clin. Immunol*., 2011, **128** : 3-20.
9. MOLINA-INFANTE J., KATZKA D.A., GISBERG J.P. Review article : Proton pump inhibitor therapy for suspected eosinophilic esophagitis. *Alliment. Pharmacol. Ther*., 2013, **37** : 300-307.
10. DELLON E.S., SPECK O., WOODWARD K., GEBHART J.H., MADANICK R.D., LEVINSON S. *et al*. Clinical and endoscopic characteristics do not reliable differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy : a prospective cohort study. *Am. J. Gastroenterol*., 2013, **108** : 1854-1860.
11. MOAWAD F.J., SCHOEPFER A.M., SAFRONEEVA E., ALLY M.R., CHEN Y.-J., MAYDONOVITCH C.L. *et al*. Eosinophilic oesophagitis and proton pump-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. *Alliment. Pharmacol. Ther*., 2014, **39** : 603-608.
12. DELLON E.S., SPECK O., WOODWARD K., COVEY S., RUSIN S., GEBHART J.H. *et al*. Markers of eosinophilic inflammation for diagnosis of eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia : a prospective study. *Clin. Gastroenterol. Hepatol*., 2014, **12** : 2015-2022.
13. MOLINA-INFANTE J., RIVAS MD., HERNANDEZ-ALONSO M., VINAGRE-RODRÍGUEZ G., MATEOS-RODRÍGUEZ JM., DUEÑAS-SADORNIL C. *et al*. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. *Alliment. Pharmacol. Ther*., 2014, **40** : 955-965.
14. WEN T., DELLON E.S., MOAWAD F.J., FURUTA G.T., ACEVES S.S., ROTHENBERG M.E. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammaton. *J. Allergy Clin. Immunol*., 2015, **135** : 187-197.
15. CHENG E. Proton pump inhibitors for eosinophilic esophagitis. *Curr. Opin. Gastroenterol*., 2013, **29** : 416-420.
16. CHENG E., ZHANG X., HUO X., YU C., ZHANG Q., WANG D.H. *et al*. Omeprazole blocks eotaxin-3 expression by esophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut*, 2013, **62** : 824-832.
17. ZHANG X., CHENG E., HUO X., YU C., ZHANG Q., PHAM T.H. *et al*. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PloS One*, 2012, **7** : e50037.
18. MERWAT S.N., SPECHLER S.J. Might the use of acid-suppresive medication predispose to the development of eosinophilic esophagitis ? *Am. J. Gastroenterol*., 2009, **104** : 1897-1902.
19. SEHGAL S., DARBARI A., BADER A. Herpex simplex virus and eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr*., 2013, **56** : e1.
20. SQUIRES K.A., CAMERON D.J., OLIVER M., DA FONESCA JACNQUEIRA J.C. Herpes simplex and eosinophilic oesophagitis : the chicken or the egg ? *J. Pediatr. Gastroenterol. Nutr*., **49** : 246-250.
21. HOMAN M., OREL R., LIACOURAS C. Caustic ingestion : a possible cause of eosinophilic esophagitis. Pediatrics, 2013, **131** : e1284-el287.
22. KATZKA D.A. The complex relationship between eosinophilic esophagitis and gastroesophageal reflux. *Dig. Dis*., 2014, **32** : 93-97.
23. WEIJENBORG P.W., SMOUT A.J., VERSEIJDEN C., VAN VEEN H.A., VERHEIJ J., DE JONGE W.J. *et al*. Hypersensitivity to acid is associated with impaired esophageal mucosal integrity in patients with gastroesophageal reflux disease with and without esophagitis. *Am. J. Physiol. Gastrointest. Liver Physiol*., 2014, **307** : G323-G329.
24. REMEDIOS M., CAMPBELL C., JONES D.M., KERLIN P. Eosinophilic esophagitis in adults : clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest. Endosc*., 2006, **63** : 3-12.
25. SHAH A., KAGALWALLA A.F., GONSALVES N., MELIN-ALDANA H., LI BU., HIRANO I. Histopathologic variability in children with eosinophilic esophagitis. *Am. J. Gastroenterol*., 2009, **104** : 716-721.
26. PETERSON K.A., THOMAS K.L., HILDEN K., EMERSON L.L., WILLS J.C., FANG J.C. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig. Dis. Sci*., 2010, **55** : 1313-1319.
27. MOLINA-INFANTE J., FERRANDO-LAMANA L., RIPOLL C., HERNANDEZ-ALONSO M., MATEOS J.M., FERNANDEZ-BERMEJO M. *et al*. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin. Gastroenterol. Hepatol*., 2011, **9** : 110-117.
28. GORTER R.R., HEIJ H.A., VAN DER VOORN J.P., KNEEPKENS C.M.F. Eosinophilic esophagitis after esophageal atresia : is there an association ? Case presentation and literature review. *J. Pediatr. Surg*., 2012, **47** : E9-E13.
29. YAMADA Y., NISHI A., KATO M., TOKI F., YAMAMOTO H., SUZUKI N. *et al*. Esophagitis with eosinophil infiltration associated with congenital esophageal atresia and stenosis. *Int. Arch. Allergy Immunol*., 2013, **161** Suppl 2, 159-163.
30. CALABRESE C., BORTOLOTTI M., FABBRI A., ARENI A., CENACCHI G., SCIALPI C. *et al*. Reversibility of GERD ultrastructural alterations and relief of symptoms after omeprazole treatment. *Am. J. Gastroenterol*., 2005, **1000** : 537-542.
31. VAN RHIJN B.D., WEIJENBORG P.W., VERHEIJ J., VAN DEN BERGH WEERMAN M.A., VERSEIJDEN C., VAN DEN WIJNGAARD R.M. *et al*. Proton pump inhibitors partially restore mucosal integrity in patients with

proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.*, 2014, **12** : 1815-1823.
32. VAN MALENSTEIN H., FARRÉ R., SIFRIM D. Esophageal dilated intercellular spaces (DIS) and nonerosive reflux disease. *Am. J. Gastroenterol.*, 2008, **103** : 1021-1028.
33. MULLIN J.M., VALENZANO MC., WHITBY M., LURIE D., SCHMIDT J.D., JAIN V. *et al*. Esomeprazole induces upper gastrointestinal tract transmucosal permeability increase. *Aliment. Pharmacol. Ther.*, 2008, **28** : 1317-1325.
34. SAFFARI H., PETERSON K.A., FANG J.C., TEMAN C., GLEICH G.J., PEASE L.F. Patchy eosinophil distributions in an esophagectomy specimen from a patient with eosinophilic esophagitis : Implications for endoscopic biopsy. *J. Allergy Clin. Immunol.*, 2012, **130** : 798-800.
35. MURCH S.H., ALLEN K., CHONG S., DIAS J.A., PAPADOPOULOU A., ANTUNES H. *et al*. Potential for improving therapy and defining new research targets in eosinophilic oesophagitis based on understanding of immunopathogenesis. *J. Pediatr. Gastroenterol. Nutr.*, 2013, **57** : 529-534.
36. UNTERSMAYR E., BAKOS N., SCHÖLL I., KUNDI M., ROTH-WALTER F., SZALAI K. *et al*. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J.*, 2005, **19** : 656-658.
37. UNTERSMAYR E., POULSEN LK., PLATZER M.H., PEDERSEN M.H., BOLTZ-NITULESCU G., SKOV P.S. *et al*. The effect of gastric digestion on codfish allergenicity. *J. Allergy Clin. Immunol.*, 2005, **115** : 377-382.
38. UNTERSMAYR E., VESTERGAARD H., MALLING H.J., JENSEN L.B., PLATZER M.H., BOLTZ-NITULESCU G. *et al*. Incomplete digestion of codfish represents a risk factor for anaphylaxis in patients with allergy. *J. Allergy Clin. Immunol.*, 2007, **119** : 711-717.
39. UNTERSMAYR E., SCHÖLL I., SWOBODA I., BEIL W.J., FÖRSTER-WALDL E., WALTER F. *et al*. Antacid medication inhibits digestion of dietary proteins and causes food allergy : a fish allergy model in BALB/c mice. *J. Allergy Clin. Immunol.*, 2003, **112** : 616-623.
40. SCHÖLL I., UNTERSMAYR E., BAKOS N., ROTH-WALTER F., GLEISS A., BOLTZ-NITULESCU G. *et al*. Anti-ulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. *Am. J. Clin. Nutr.*, 2005, **81** : 154-160.
41. YU Y.H., HAN D.S., CHOI E.Y., PARK H.S., JEONG J.Y., EUN C.S., OH Y.H. *et al*. Is use of PPIs related to increased intraepithelial lymphocytes in the colon ? *Dig. Dis. Sci.*, 2012, **57** : 2669-2674.
42. TURK H., HAUSER B., BRECELJ J., VANDENPLAS Y., OREL R. Effect of proton pump inhibition on acid, weakly acid and weakly alkaline gastro-esophageal reflux in children. *World J. Pediatr.*, 2013, **9** : 36-41.
43. VELA M.F., CAMACHO-LOBATO L., SRINIVASAN R., TUTUIAN R., KATZ P.O., CASTELL D.O. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux : effect of omeprazole. *Gastroenterology*, 2001, **120** : 1588-1598.
44. HEMMINK G.J., BREDENOORD A.J., WEUSTEN B.L., MONKELBAAN J.F.,TIMMER R., SMOUT A.J. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms : 'on' or 'off' proton pump inhibitor ? *Am. J. Gastroenterol.*, 2008, **103** : 2446-2453.
45. FRAZZONI M., SAVARINO E., MANNO M., MELOTTI G., MIRANTE V.G., MUSSETTO A. *et al*. Reflux patterns in patients with short-segment Barret's oesophagus : a study using impedance-pH monitoring off and on proton pump inhibitor therapy. *Aliment. Pharmacol. Ther.*, 2009, **30** : 505-515.
46. ORR W.C., CRADDOCK A., GOODRICH S. Acidic and non-acidic reflux during sleep under conditions of powerful acid suppression. *Chest*, 2007, **131** : 460-465.
47. SANAKA M., YAMAMOTO T., KUYAMA Y. Effects of proton pump inhibitors on gastric emptying : a systematic review. *Dig. Dis. Sci.*, 2010, **55** : 2431-2440.