Healing of Erosive Esophagitis and Improvement of Symptoms of Gastroesophageal Reflux Disease After Esomeprazole Treatment in Children 12 to 36 Months Old

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ABSTRACT

Objectives: The aim of the study was to evaluate erosive esophagitis healing and symptom improvement with once-daily esomeprazole in children ages 12 to 36 months with endoscopically or histologically proven gastroesophageal reflux disease (GERD).

Patients and Methods: Data from children ages 12 to 36 months were included in a post-hoc analysis of an 8-week, multicenter, randomized, and double-blind by dose strata study of patients ages 1 to 11 years with endoscopically or histologically confirmed GERD. Children were randomized to receive esomeprazole 5 or 10 mg once daily. Patients underwent endoscopy and, if required, mucosal biopsy at baseline. Patients who had erosive esophagitis (graded using the Los Angeles classification system) at baseline underwent a follow-up endoscopy at final study visit to assess healing of erosive esophagitis. Investigators scored severity of GERD symptoms at baseline and every 2 weeks using the Physician Global Assessment.

Results: Thirty-one of 109 primary study patients ages 12 to 36 months were included in the post hoc analysis. At baseline, 15 patients (48.4%) had erosive esophagitis, underwent follow-up endoscopy, and were healed after 8 weeks of esomeprazole treatment. Of the 19 patients with moderate-to-severe baseline Physician Global Assessment symptom scores, 84.2% had lower scores by the final visit. Following esomeprazole treatment, GERD symptoms were significantly improved from baseline to final visit ($P \leq 0.0018$).

Conclusions: Esomeprazole 5 or 10 mg may be used to successfully treat erosive esophagitis and symptoms of GERD in children as young as 1 year. Moreover, although not yet validated in pediatric patients, the Los Angeles classification system was useful in grading erosive esophagitis in children ages 12 to 36 months.

Key Words: erosive esophagitis, esomeprazole, proton pump inhibitor

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Gastroesophageal reflux disease (GERD) is becoming recognized as a common pediatric disorder (1) that can lead to erosive esophagitis, even in the younger age groups (2–4). Results of a retrospective study estimated the incidence of GERD in children younger than 5 years to be 0.91/1000 person-years and the mean age at initial diagnosis of children younger than 5 years to be 7.3 months (5). A recent retrospective cross-sectional study of 12 children's hospitals in the United States using the Pediatric Endoscopy Database System-Clinical Outcomes Research Initiative determined that 9.5% of children ages 1 year and 7.6% of children ages 2 years had erosive esophagitis (4). In addition, data from a study conducted at a single center in the United States showed that nearly 30% of patients between the ages of 18 months and 5 years with GERD who underwent endoscopy had erosive esophagitis (6).

Physiological GER in infants may lead to pathological GERD during childhood, which often persists into adolescence and adulthood (7). Symptoms of reflux vary depending on the child's age. Preadolescent children often experience heartburn, epigastric pain, abdominal pain, regurgitation, and intermittent vomiting (1,8–10). Infants and toddlers, however, more commonly experience regurgitation and feeding difficulties (1,11). A thorough history and physical examination should be performed to differentiate uncomplicated GER, which does not require pharmacological therapy, from GERD or other diagnoses. If recurrent vomiting is accompanied by symptoms of poor weight gain, excessive crying, irritability, disturbed sleep, feeding, or respiratory problems, or if symptoms are persistent despite using a hypoallergenic formula or empirical acid suppression, then additional diagnostic tests may be required (1).

Proton pump inhibitors (PPIs) are a recommended therapy in pediatric patients by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines (1). Treatment with esomeprazole has been shown to be effective in healing erosive esophagitis and resolving GERD symptoms in adults (12–14) and in children ages 1 to 11 years (2,3). The pharmacokinetic profile, tolerability, and clinical outcome of esomeprazole in patients ages 1 to 17 years with symptoms of GERD have been reported previously (2,3,15,16). Esomeprazole

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is approved in the United States, Canada, Australia, and several European countries for the treatment of GERD in patients ages 1 to 17 years.

In this post-hoc analysis of 1 of the largest studies to date using PPIs for this age group, the healing of erosive esophagitis and improvement in GERD symptoms from baseline after 8 weeks of esomeprazole treatment were assessed in children ages 12 to 36 months with endoscopically proven GERD**.** The safety and clinical outcomes of esomeprazole treatment of GERD in the primary study population of children ages 1 to 11 years have been reported previously (2,3).

PATIENTS AND METHODS

Study Design and Patients

Institutional review boards from all of the participating sites approved the protocol. Each patient's parent or guardian provided written informed consent before any study-specific procedure was performed. The study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments and with the International Conference on Harmonization Good Clinical Practice guidelines.

This parallel-group, randomized and double-blind by dose strata, 8-week study was conducted at 24 sites in the United States (15 sites, n = 82), France (2 sites, n = 7), Belgium (3 sites, n = 7), and Italy (4 sites, n = 10). The methods were described previously in detail (2). Briefly, the primary study population included children ages 1 to 11 years inclusive who had received a diagnosis of GERD confirmed endoscopically or histologically based on standard medical care, weighed 8 kg or more, and were considered candidates for PPI therapy by the investigator. Patients were excluded if they had endoscopic findings of advanced esophageal lesions (ie, strictures or Barrett esophagus) caused by GERD or other severe upper gastrointestinal (GI) tract pathology, history or current need for resectional or reconstructive surgery of the GI tract, or other significant GI pathology.

Patients were not allowed to use a PPI within 7 days or an H_2-receptor antagonist or prokinetic agent within 3 days of randomization. Antacids were permitted, except for those containing bismuth.

Eligible patients received treatment for 8 weeks in a double-blind by dose strata fashion based on their weight at screening. Patients weighing 8 to <20 kg were randomized 1:1 to receive esomeprazole 5 or 10 mg daily. Patients weighing ≥20 kg were randomized 1:1 to receive esomeprazole 10 or 20 mg daily. All of the children ages 12 to 36 months were randomized to esomeprazole 5 or 10 mg daily and were included in the post hoc analysis. Study medication was administered 60 minutes before breakfast. The capsule contents could be mixed with 1 to 2 tablespoons of applesauce for children younger than 6 years or for those who had difficulty swallowing the capsules. Age-appropriate liquid antacid medication, such as Maalox (aluminum hydroxide 225 mg/magnesium hydroxide 200 mg/5 mL; Novartis Consumer, Parsippany, NJ), was provided as rescue medication.

Assessments

During the screening period, the physician obtained the patients' medical history, vital signs, a physical examination, the Physician's Global Assessment (PGA) of the patient's overall GERD-related symptoms during the last 7 days, GERD-related symptoms during the last 72 hours from the caregiver, and laboratory assessments. Additionally, the physician determined whether the patient was eligible for inclusion based on the study inclusion/exclusion criteria.

Moreover, each patient underwent an upper GI endoscopy during the screening period to document the extent of esophagitis, determine the presence of *Helicobacter pylori* or any other gastric or duodenal pathology, and, when clinically appropriate, to identify exclusionary esophageal conditions, such as eosinophilic esophagitis, ulcers, or bleeding lesions. An endoscopy was not required if the patient had a previous endoscopic diagnosis of reflux-induced esophagitis within 2 weeks of screening and was a candidate for PPI therapy. If a patient did not require an endoscopy or did not have esophagitis, then he or she was not eligible for study entry. For patients with erosive esophagitis at baseline, a follow-up endoscopy was performed at the final study visit to assess healing. Endoscopic findings were graded using the Los Angeles (LA) classification for erosive esophagitis (17). Grade A is ≥1 mucosal break <5 mm that does not extend between the tops of 2 mucosal folds, grade B is ≥1 mucosal break >5 mm that does not extend between the tops of 2 mucosal folds, grade C is ≥1 mucosal break that is continuous between the tops of ≥2 mucosal folds but that involves <75% of the circumference, and grade D is ≥1 mucosal break that involves ≥75% of the circumference. In addition, other pediatric endoscopic GERD descriptors of esophagitis, such as hyperemia, ulcers, and nodularity, were used and, when indicated, histological evaluation was performed (4,18). Collection of biopsy specimens was not a study requirement and was performed only as part of the standard of care at the discretion of the GI specialist. In patients without visible or definitive lesions, mucosal biopsy specimens were obtained during baseline endoscopy for histological confirmation of GERD-related esophagitis (19). In this report, we present a descriptive summary of endoscopic and histologic findings as collected in the present study population as background to the erosive esophagitis healing data.

Throughout the study, parents/guardians called into the Interactive Voice Response System at approximately the same time each day to report the presence and severity of their child's GERD-related symptoms based on the previous 24-hour period. Symptoms and signs were derived from the original version of the recently updated North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines (1,20), which recognize that GERD presentation varies by pediatric age group. Therefore, certain symptoms may not be reportable in younger toddlers. Symptoms included regurgitation, abdominal pain, vomiting, eating difficulties, and difficulty swallowing. Investigators completed the PGA on the overall clinical impression of their patient's GERD-related symptoms as none (no symptoms), mild (symptoms present but not interfering with daily activities), moderate (symptoms present and somewhat interfering with daily activities), or severe (symptoms present and greatly interfering with or preventing daily activities) during the 7 days before baseline and then every 2 weeks after randomization.

Statistical Analysis

This post-hoc analysis only included patients ages 12 to 36 months from the intention-to-treat population dataset. The intention-to-treat population included patients who had a baseline and at least 1 postbaseline measurement for the appropriate endpoint investigated and who took 1 or more doses of study medication. The percentage of patients with healed erosive esophagitis, defined as no sign of erosion on final endoscopy, was determined at study completion. Baseline PGA scores were compared with each biweekly assessment using a Cochran-Mantel-Haenszel χ^2 test

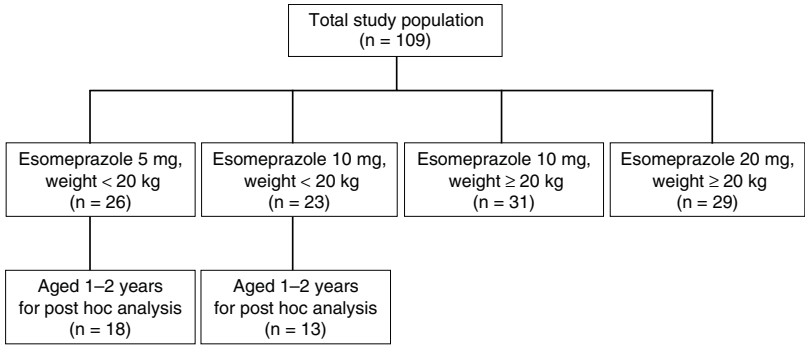

FIGURE 1. Patient disposition.

within each dose group separately. Differences between the 5- and 10-mg dose groups were not assessed.

RESULTS

Of the 109 patients randomized into the primary study (2), a total of 31 patients were 12 to 36 months of age (all weighing <20 kg) and were included in this analysis (Fig. 1; Table 1). None of the patients had any noteworthy comorbid diseases, and 11 patients had received an endoscopy before screening. Before randomization, 4 patients had previously received treatment with an H_2-receptor antagonist and 5 patients had previously received treatment with a PPI. Most patients were girls (58.1%) and white (74.2%). Of these 31 patients, 15 (48.4%) had erosive esophagitis (Table 1) and 23 (74.2%) had microscopic (not visible) reflux esophagitis based on baseline biopsy data, not mutually exclusive. Nonerosive endoscopic findings were documented in 4 patients (12.9%) with hiatal hernia and 14 patients (45.2%) with other esophageal abnormalities (eg, distal esophageal hyperemia, nodularity, atypical ulcers not consistent with classical erosive esophagitis). These findings were not mutually exclusive (Table 1). Baseline histological findings are presented in Table 2. At baseline, more than half of the patients had

TABLE 1. Demographic and baseline clinical and endoscopic characteristics

Characteristic	Esomeprazole 5 mg (n = 18)	Esomeprazole 10 mg (n = 13)	Total (N = 31)
Female sex	10 (56)	8 (62)	18 (58)
Age group, mo			
12–23	12 (67)	8 (62)	20 (65)
24–36	6 (33)	5 (39)	11 (36)
Mean (range) age, mo	21.8 (13–33)	22.5 (14–35)	22.1 (13–35)
Race			
White	14 (78)	9 (69)	23 (74)
Black	4 (22)	4 (31)	8 (26)
Mean (range) height, cm	85.3 (70–103)	86.4 (80–103)	85.8 (70–103)
Mean (range) weight, kg	11.5 (8–16)	12.1 (10–16)	11.7 (8–16)
Mean (SD) body mass index, kg/m^2	15.8 (2.3)	16.2 (1.5)	15.9 (2.0)
Erosive esophagitis	10 (56)	5 (39)	15 (48)
LA grade A	5 (28)	3 (23)	8 (26)
LA grade B	5 (28)	1 (8)	6 (19)
LA grade C	0	1 (8)	1 (3)
LA grade D	0	0	0
Symptoms at baseline			
Heartburn	10 (56)	6 (46)	16 (52)
Regurgitation	14 (78)	6 (46)	20 (65)
Abdominal pain	10 (56)	7 (54)	17 (55)
Vomiting	11 (61)	5 (39)	16 (52)
Eating difficulties	10 (56)	9 (69)	19 (61)
Difficulty swallowing	4 (22)	4 (31)	8 (26)
Other esophagitis*	8 (44)	8 (62)	16 (52)
Hiatal hernia	3 (17)	1 (8)	4 (13)
Mean (range) esomeprazole dose, mg/kg	0.5 (0.3–0.6)	0.8 (0.6–1.0)	0.6 (0.3–1.0)

All of the values are n (%) unless otherwise noted. LA = Los Angeles classification.
* Other endoscopic descriptors of reflux esophagitis: nodularity, hyperemia, and/or histological confirmation.

TABLE 2. Baseline histological data

Characteristic, n (%)	Esomeprazole 5 mg (n = 18)	Esomeprazole 10 mg (n = 13)	Total* (N = 31)
Eosinophilic densification	4 (22.2)	1 (7.7)	5 (16.1)
Intraepithelial eosinophils per HPF	3 (16.7)	6 (46.2)	9 (29.0)
Intraepithelial neutrophils per HPF	3 (16.7)	0	3 (9.7)
Intraepithelial lymphocytes per HPF	9 (50.0)	4 (30.8)	13 (41.9)
Elongated length of papillae	11 (61.1)	6 (46.2)	17 (54.8)
Increased thickness of basal cell layer	9 (50.0)	9 (69.2)	18 (58.1)
Increased total epithelial thickness	8 (44.4)	7 (53.8)	15 (48.4)
Dilation of intercellular spaces			
<25%	2 (11.1)	0	2 (6.5)
≥25%	2 (11.1)	0	2 (6.5)
Columnar epithelium assessable	2 (11.1)	1 (7.7)	3 (9.7)
Cardia mucosa	1 (5.6)	1 (7.7)	2 (6.5)

HPF = high-power field.
* Includes patients with erosive and nonerosive esophagitis at baseline.

symptoms of heartburn, acid regurgitation, abdominal pain, vomiting, and feeding difficulties (Table 1).

Of the 15 patients with erosive esophagitis at baseline, 13 patients were available to complete the endoscopy and were included in the healing analysis. All of the patients who had erosive esophagitis at baseline and who underwent posttreatment endoscopy were healed after 8 weeks of esomeprazole treatment. Of the 19 patients with moderate or severe baseline PGA symptom scores, 16 (84.2%) had improved scores by the final visit (Fig. 2). In addition, a statistically significant reduction ($P \leq 0.0018$) was seen in the severity of GERD symptoms within each treatment group from baseline to the final PGA assessment (2).

The mean use of rescue medication was similar across all of the treatment groups. The average use was <3/4 teaspoon per day of aluminum hydroxide 225 mg/magnesium hydroxide 200 mg/5 mL.

All doses of esomeprazole used daily generally were well tolerated (2). The most common adverse events in the overall study population of children ages 1 to 11 years with GERD were vomiting, pyrexia, and diarrhea (2).

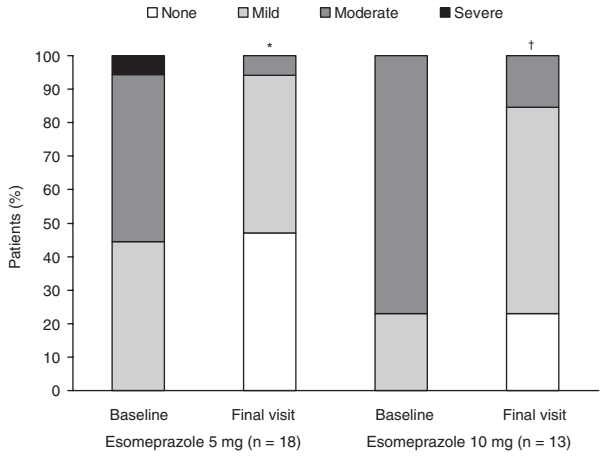

FIGURE 2. Physician's Global Assessment. Frequency distribution of symptom severity at baseline and at final visit. *$P = 0.0001$ vs baseline, †$P = 0.0018$ vs baseline.

DISCUSSION

Although several previous studies have reported on symptoms and outcomes in older children (1–3,8,9,12), few data on toddlers ages 12 to 36 months with GERD and erosive esophagitis are available. In this post-hoc analysis among the largest population to date in this age group, erosive esophagitis was healed after 8 weeks of esomeprazole treatment in all of the children ages 12 to 36 months who had the condition at baseline and received a follow-up endoscopy. In addition, a significant number of patients who had moderate or severe baseline PGA symptom scores experienced improvement in GERD symptoms after treatment. In this analysis, toddlers had endoscopically or histologically confirmed GERD and the majority of those who received acid-suppressive therapy demonstrated significant symptom improvement from baseline.

After 8 weeks of treatment with esomeprazole, erosive esophagitis was healed and symptoms improved from baseline in the present group of toddlers. Similarly, treatment with pantoprazole 0.3 or $1.2\,mg \cdot kg^{-1} \cdot day^{-1}$, but not with pantoprazole $0.6\,mg \cdot kg^{-1} \cdot day^{-1}$, for 8 weeks significantly improved GERD symptoms from baseline ($P < 0.001$) in a recent study of 60 young children ages 1 to 5 years (21). Additionally, a study of lansoprazole 15 or 30 mg daily in 66 children ages 1 to 11 years showed that symptoms improved significantly from baseline and all of the children with erosive esophagitis at baseline (n = 28) were healed after 12 weeks of treatment (22). A subanalysis of children ages 12 to 36 months was not reported from the present study (22). In the absence of a control group in the present study, spontaneous healing cannot be ruled out. Additionally, a previously conducted study suggested that irrespective of maintenance treatment with omeprazole, ranitidine, or no treatment, there was a low incidence of erosive esophagitis relapse and GERD symptom recurrence in 48 children ages 32 to 170 months following healing with omeprazole (23). The present study did not assess whether continued treatment with esomeprazole beyond the 8 weeks of treatment is necessary, and this is an area of future research.

The symptoms in this group of patients were similar to those experienced by the patients ages 1 to 11 years in the primary study population (2,3) and by children in other studies (1,8–10). Compared with older children, symptoms of regurgitation and feeding difficulties are more common in infants and toddlers (1). In the primary study, more children weighing <20 kg (ages 1–6 years) had symptoms of vomiting, eating or feeding difficulties, and

difficulty swallowing compared with children weighing ≥20 kg (ages 4–11 years) (2). In this analysis, the most commonly reported symptoms at baseline were regurgitation, eating difficulties, and abdominal pain. Also consistent with the primary study population, erosive esophagitis was a common finding in approximately half of the patients in this post-hoc analysis, with most having LA grades A or B erosive esophagitis (3). Although erosive esophagitis generally is not common in the pediatric age group, in our study of 31 toddlers, it was prevalent. In comparison, the prevalence of erosive esophagitis in children ages 12 to 36 months from another multicenter database was 9.5% and 7.6%, respectively (4). Although the reasons for a higher prevalence of erosive esophagitis in the present study are not clear, 1 possible explanation is the selection of sicker patients. This selection bias may be due to enrollment of patients who have not responded satisfactorily to other approved therapy. Other factors that may predispose pediatric patients to erosive esophagitis include hiatal hernia (4) and sinus, pharyngeal, laryngeal, and pulmonary diseases (24,25) including cystic fibrosis, and neurologic conditions including cerebral palsy (10). The current pediatric literature includes few reports of the use of PPIs for the treatment of erosive esophagitis (2,3,26,27), and the present study contributes a large published patient case series in children younger than 3 years with erosive esophagitis.

Although the Montréal and recently published pediatric definition of GERD allow for diagnosis based on characteristic symptoms without diagnostic techniques (1,25,28), esophageal biopsy in children, including toddlers, is recommended during diagnostic endoscopy because a poor correlation exists between endoscopic appearance and histopathology (1). In addition, other potential coexisting or alternative diagnoses, such as eosinophilic esophagitis or GI allergies, need to be excluded for optimal management. In this analysis, patients with no visible or definitive lesions underwent a mucosal biopsy to histologically confirm GERD-related esophagitis. Moreover, histological characteristics may not correlate with symptom improvement, and it is not known whether mild histological changes occur in asymptomatic physiological GER or how long histological changes persist after adequate control and improvement in GERD symptoms.

The histological characteristics of GERD and erosive esophagitis in young children are not well documented. In the children ages 12 to 36 months who were analyzed here, approximately half had elongated papillae (55%), increased thickness of the basal cell layer (58%), and increased total epithelial thickness (48%) reported in their histology specimens. Many patients also had intraepithelial eosinophils (30%) and lymphocytes (42%). These histological abnormalities have been shown to be markers of acid reflux in children (1,19,29–31). In addition, nearly 75% of the patients in this analysis had concomitant findings of microscopic reflux esophagitis, such as intraepithelial eosinophils, neutrophils, morphometric measures of increased basal cell layer thickness, and increased papillary height.

The LA classification system is used routinely in studies of adults with erosive esophagitis (17). Although this system has not been validated yet in pediatric patients (1), it was used in this analysis to grade the severity of erosive esophagitis. The need remains for a complementary scoring system that accommodates other pediatric endoscopic and histological findings.

In conclusion, the results of this post-hoc analysis add to the limited body of literature on GERD and erosive esophagitis in young children. After 8 weeks of esomeprazole treatment, erosive esophagitis was healed in all of the children ages 12 to 36 months who had erosive esophagitis at baseline and underwent a follow-up endoscopy. Also, most patients who had moderate or severe GERD symptoms at baseline had improvement in symptoms after esomeprazole treatment. These results suggest that esomeprazole 5 or 10 mg is successful in treating erosive esophagitis and the symptoms of GERD in children as young as 1 year. Moreover, the LA classification system was useful in grading erosive esophagitis in these young children; however, further validation in children is needed.

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