

ORIGINAL ARTICLE

Enteryx implantation for GERD: expanded multicenter trial results and interim postapproval follow-up to 24 months

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Background: Enteryx implantation in the esophagus is an alternative therapy for patients with proton pump inhibitor (PPI) dependent GERD. Although this treatment resulted in highly significant improvement at 6 and 12 months, longer follow-up is needed to more fully assess the durability of these positive effects.

Methods: An open-label, international clinical trial was conducted in 144 PPI-dependent patients with GERD with follow-up at 6 and 12 months. In addition, the durability and the safety of the treatment were assessed for 24 months in 64 patients enrolled in a postapproval study. The primary study outcome measure was usage of PPI. Secondary outcomes in the multicenter trial were symptom response GERD health-related quality of life (GERD-HRQL) and esophageal acid exposure.

Results: At 12 months, PPI use was reduced $\geq 50\%$ in 84%: 95% confidence interval (CI) [76%, 90%] and was eliminated in 73%: 95% CI[64%, 81%] of evaluable patients (intent-to-treat analysis 78%: 95% CI[70%, 84%] and 68%: 95% CI[60%, 76%], respectively). A GERD-HRQL ≤ 11 was attained in 78%: 95% CI[69%, 85%] of evaluable patients. Esophageal acid exposure (total time pH < 4) was reduced by 31%: 95% CI[17%, 43%]. At 24 months, a $\geq 50\%$ or greater reduction in PPI use was achieved in 72%: 95% CI[59%, 82%] and PPI use was eliminated in 67%: 95% CI[54%, 78%] of patients.

Conclusions: This investigation provides evidence for sustained effectiveness and safety of implantation of Enteryx in the esophagus in PPI-dependent patients with GERD. (Gastrointest Endosc 2005; ■: ■-■.)

GERD is a chronic condition that results from retrograde flow of gastric content into the esophagus. Minimally invasive endoluminal therapy has recently become a treatment option for patients with GERD. One such approach is implantation of Enteryx (Microvasive Endoscopy, Boston Scientific Corp., Natick, Mass.), a non-resorbable, biocompatible copolymer that is implanted into the deep mural tissue of the lower esophageal sphincter (LES).¹ Enteryx is injected as a nonviscous liquid by using a sclerotherapy-type needle under fluoroscopic visualization. The material solidifies rapidly in situ and is presumed to act by modifying distensibility and compliance at the cardioesophageal junction, thereby preventing gastroesophageal reflux.² The long-term durability of the implant has been demonstrated in a porcine model,² and

early reports of studies of the clinical effectiveness and the safety of Enteryx have been encouraging.^{1,3-6}

The results of our multicenter international clinical trial that evaluated the 12-month results of Enteryx implantation in 85 patients with GERD have been reported.⁴ Subsequently, 59 additional patients were treated under an identical protocol. This report summarizes the final 12-month effectiveness and safety data for the expanded population of 144 patients enrolled under the protocol. Also reported are the available results for durability and long-term safety in 64 of these patients, who have been followed for at least 24 months in a postapproval study.

PATIENTS AND METHODS

Study design

The multicenter trial was conducted at 8 study centers in the United States, Canada, and Belgium. The trial population size was chosen to provide 80% power in

115 detecting a 25% reduction in median proton pump
116 inhibitor (PPI) use at the 0.05 α level.

117 As required by the U.S. Food and Drug Administration
118 (FDA), a 36-month postapproval study exclusively enroll-
119 ing patients from the United States has been commenced
120 to evaluate the durability and the long-term safety of the
121 Enteryx implantation procedure. The target total enroll-
122 ment of 300 patients was selected to ensure a half-width
123 no greater than 6% for the 95% confidence interval (CI)
124 around the adverse event rate. Up to 100 patients from
125 the multicenter trial and 200 new patients are eligible to
126 enter the postapproval study; 85 from the multicenter trial
127 have been accrued to date. Interim results are presented
128 in this report for 64 of these patients who have been
129 followed for at least 24 months.

131 Outcomes

132 The primary study outcome measure was PPI usage.
133 Patients were judged to be treatment responders if PPI use
134 was eliminated or reduced 50% or more after Enteryx
135 implantation. Additional effectiveness outcomes assessed
136 were the following: GERD symptoms, quality of life scores,
137 esophageal acid exposure, and esophageal manometric
138 parameters. Safety was assessed by determination of the
139 frequency of adverse events.

142 Patient eligibility

143 The major eligibility criteria were the following: (1)
144 history of heartburn and/or regurgitation necessitating
145 continuous daily use of PPI for 3 months or more before
146 study entry and (2) increased esophageal acid exposure
147 (time pH < 4: total \geq 5%, supine \geq 3%). Patients entered
148 the trial if their symptoms were well controlled and
149 symptom scores normalized with PPI therapy, and
150 returned to abnormal levels within 10 days of PPI
151 withdrawal. GERD symptoms were assessed by using the
152 validated GERD health-related quality of life (GERD-
153 HRQL) score.⁷ Symptom response was defined by
154 a GERD-HRQL score of 11 or less,⁷ whereas an increase
155 in the score of 9 or greater vs. baseline while taking a PPI
156 was considered indicative of recurrence. Exclusion criteria
157 were the following: (1) significant impairment of esoph-
158 ageal body motility (>50% ineffective peristalsis); (2)
159 previous gastric or esophageal surgery; (3) serious
160 systemic disease; (4) scleroderma; (5) erosive esophagitis
161 of grade III or greater (Savary-Miller); (6) Barrett's
162 esophagus; (7) hiatus hernia 3 cm or longer, as deter-
163 mined at endoscopy; (8) body mass index (BMI) of 35
164 kg·m⁻² or greater; (9) an autoimmune disorder requiring
165 treatment within the preceding 2 years; (10) esophageal
166 or gastric cancer; (11) esophageal or gastric varices; (12)
167 use of anticoagulants other than 325 mg aspirin or
168 equivalent per day; (13) pregnancy; and (14) unwilling-
169 ness to participate in all follow-up evaluations. The
170 protocol was approved at each center, either through an

Capsule Summary

What is already known on this topic

- Implantation of a nonresorbable copolymer (Enteryx) into the muscle of the gastroesophageal junction improves GERD symptoms and quality of life and reduces or eliminates PPI use.

What this study adds to our knowledge

- In an open-labeled, multicenter trial, Enteryx eliminated PPI use in ~70% of patients, and normalized GERD-related quality of life is ~78% at 12 months.
- At 24 months after Enteryx implantation, 67% of patients are off PPI therapy.

187 institutional review board or an ethics committee. In-
188 formed written consent was obtained in all patients.

190 Pre- and posttreatment evaluation

191 Patient evaluation in the multicenter trial consisted of
192 the following: a medical history, including medication use,
193 GERD-HRQL score, SF-36 (Short Form with 36 questions)
194 quality of life score,⁸ prolonged (\geq 12 hours) esophageal
195 pH monitoring, esophageal manometry, barium contrast
196 esophagram, chest radiograph, upper endoscopy, record-
197 ing of adverse events, and a patient diary. Follow-up
198 evaluations were performed at 1, 3, 6, and 12 months after
199 Enteryx implantation. The fractional volume of residual
200 implant at 12 months was assessed based upon a non-
201 blinded review by the individual investigators. Residual
202 implant volume was approximated by quartile, when using
203 the 1-month posttreatment radiograph as a baseline. For
204 the participants in the postapproval study, PPI usage,
205 GERD-HRQL score, and adverse events were assessed for
206 at least 24 months.

209 Enteryx implantation

210 The nonresorbable copolymer, Enteryx, was implanted
211 as previously described.⁴ Patients with incomplete symp-
212 tom relief (GERD-HRQL score > 15 at the 1-month visit)
213 were eligible for re-treatment at the discretion of the
214 investigator. All re-treatments were completed before the
215 3-month visit.

217 Statistical analysis

218 Rates of PPI usage at 12 months and 24 months were
219 calculated per protocol as the percentage of evaluable
220 patients. In addition, 12-month rates by intent-to-treat
221 analysis were computed as the percentage of all enrolled
222 patients, with those lost to follow-up scored as failures
223 and with the last observation carried forward in the case of
224 patients still being followed at study closure. Correspond-
225 ing exact binomial CIs also were calculated. In addition,
226 PPI usage was evaluated by the Kaplan-Meier product-limit

method. This method assesses the entire period during which patients are at risk for treatment failure, and it appropriately accounts for censoring of patients from loss to follow-up and expiration of the observation period. The Kaplan-Meier analysis was conducted by using the detailed medication histories of the patients during follow-up, including the starting and ending dates for each episode of PPI use, and the type and the dose of PPI used. Because it was possible to resume or to increase PPI usage temporarily and subsequently reduce or cease PPI therapy, an individual patient might be at risk and treatment might fail more than once. Consequently, Kaplan-Meier analyses were performed both for time to first failure and also to all failures.

Median improvements in symptoms, quality of life, and esophageal acid exposure and corresponding CI were calculated by exact Hodges-Lehmann estimation. The postimplantation stability of symptom scores was assessed by the exact Page test, an omnibus test for trend not requiring Bonferroni or other adjustment for multiple comparisons. Differences in symptom improvement between responders and nonresponders were evaluated by the exact Wilcoxon test. Potential predictors of implant outcome were evaluated by logistic regression. The mean and the standard deviation were calculated as descriptive statistics for symmetrically distributed continuous data, otherwise, the median and the interquartile range are presented. Because this is a descriptive study, there is no adjustment of *p* values or to CIs to reflect the fact that multiple statistical techniques were performed on data arising from individual patients. All CIs are 95% CIs.

Data were analyzed by using several statistical software packages (SAS version 8, SAS Institute Inc., SAS Campus Drive, Cary, N.C.; Stata 8.1, Stata Corp., College Station, Tex.; StatXact 5.03, Cytel Software Corp., Cambridge, Mass.).

RESULTS

A total of 144 patients were enrolled in the multicenter trial. Demographic characteristics and baseline medication usage of the study population are summarized in Table 1. The trial was closed before completion because of the approval of the Enteryx injection procedure by the FDA. At trial closure, 144 patients had been treated, of whom, 118 were evaluable at 12 months. Although PPI usage was assessed for all 118 evaluable patients at baseline and 12 months, complete data were not obtained for several other outcomes. Specifically, evaluable paired baseline and 12-month results were available for a GERD-HRQL score in 114 patients, esophageal manometry and ambulatory pH in 102, and esophagitis grade in 107 patients. From the postapproval study, 24-month results were secured for 64 patients.

TABLE 1. Baseline patient data in multicenter trial

Characteristic	Mean	SD
Age (y)	48	12
Body mass index (kg·m ⁻²)	28	3.9
Duration of acid reduction therapy (mo)	22	26
	n	%
Men	88	61
Women	56	39
Acid reduction therapy		
Proton pump inhibitor*		
½ standard dose	5	3.5
Standard dose	106	74
≥2 × standard dose	32	22
Supplementary H ₂ antagonists		
Less than daily	1	0.7
Daily	7	4.9
Twice per day	4	2.8
Supplementary antacids		
Less than daily	14	9.7
Daily	4	2.8
Twice per day	0	0.0

SD, Standard deviation.

*Omeprazole, pantoprazole, lansoprazole, rabeprazole, or esomeprazole; standard doses of these medications were 20, 40, 30, 20, and 40 mg, respectively.

Twenty-one patients (15% of study population) who did not fulfill one or more of the selection criteria were permitted to enter the trial. These protocol deviations totaled 27 and consisted of the following: hiatus hernia 3 cm or greater in length (*n* = 12), absence of symptom recurrence while not taking a PPI (*n* = 5), treatment with PPI for less than 3 months at entry (*n* = 3), BMI 35 kg·m⁻² or greater (*n* = 2), significant impairment of peristalsis (<50% effective; *n* = 2), inadequate esophageal acid exposure (*n* = 1), erosive esophagitis (Savary-Miller grade >III, *n* = 1), and Barrett's esophagus (*n* = 1). Deviations occurred at 6 of the 8 study centers (median frequency 2.5 per center [0.5-5]).

The average procedure time, defined as the time from endoscope insertion to removal, was 31 (16) minutes. Total fluoroscopy time was 10 (7) minutes. The mean volume of implanted Enteryx was 6.9 (1.8) mL. At 12 months, the mean residual implant volume was 67% (34%), based upon unblinded assessment by the investigators. Thirty-seven patients (26%) underwent a repeat

TABLE 2. Outcomes with respect to PPI usage

Category	Evaluable at 12 mo			Intent to treat at 12 mo			Evaluable at 24 mo		
	n	Rate* (%)	CI (%)	n	Rate* (%)	CI (%)	n	Rate* (%)	CI (%)
Responders	99	84	76-90	112	78	70-84	46	72	59-82
Off all PPIs	86	73	64-81	98	68	60-76	43	67	54-78
Dose reduced \geq 50%	13	11	6.0-18	14	9.7	5.4-16	3	4.7	1.0-13
Nonresponders	19	16	10-24	32†	22	16-30	18	28	18-41
Dose reduced < 50%	1	0.8	0.0-4.6	1	0.7	0.0-3.8	1	1.6	0.0-8.4
Dose unchanged	16	14	8.0-21	20	14	8.7-21	15	23	14-36
Dose increased	2	1.7	0.2-6.0	2	1.4	0.2-4.9	2	3.1	0.4-11

CI, Confidence interval; PPI, proton pump inhibitor.

*Based on 118 evaluable patients at 12 mo, 144 enrolled patients at 12 mo, and 64 evaluable patients at 24 mo.

†Nine of these patient were lost to follow-up.

implantation procedure within 1 to 3 months of the original treatment. Of the re-treatments, 18 (49%) were performed per protocol for inadequate symptom response (GERD-HRQL > 15), whereas the remainder were deviations from the study protocol because of either an incomplete symptom response, despite a GERD-HRQL score of 15 or less (n = 10, 27%), or an estimated residual implant volume of less than 25% (n = 9, 24%).

PPI usage

Outcomes with respect to PPI usage are summarized in Table 2. Patients who responded to treatment, i.e., those with a 50% or greater reduction in PPI dose, constituted 84% of the trial population at 12 months per protocol and 78% by intent-to-treat analysis. Cessation of PPI usage was achieved in 73% of patients per protocol and 68% by intent-to-treat analysis. In 16 of the 19 patients who did not respond to treatment, the dose of PPI remained unchanged, whereas in two patients, the PPI dose was increased after Enteryx implantation.

Exclusion of the 21 patients with protocol deviations had a negligible effect on treatment response. Thus, with these patients excluded, the proportion of patients who responded to treatment at 12 months (85%: CI[76%, 91%]) closely coincided with the 84% from the per protocol analysis without the exclusions.

Compared with the intent-to-treat response rate of 78% at 12 months, the Kaplan-Meier estimated fraction was 73% at 12 months in the multicenter trial. Most treatment failures occurred within the first 4 months after implantation (Fig. 1A). Similarly, for most patients in whom cessation of PPI usage was not achieved, resumption of usage occurred within 4 months (Fig. 1B). Thereafter, Kaplan-Meier estimated fractions remained relatively stable, with the estimate of a 50% or greater reduction in PPI usage declining by 3.9% from 4 months to 12 months and the estimate of PPI cessation declining by

2.5%. The Kaplan-Meier estimated fractions shown in Figure 1 are calculated on a time-to-first-failure basis. With all failures taken into account, the 12-month estimates of a 50% or greater reduction in PPI usage (72%: CI[63%, 78%]) and cessation of PPI usage (60%: 95% CI[52%, 68%]) were both lower by 1% than those in Figure 1.

At 12 months, 28 multicenter trial patients (24%) were taking antacids on an as needed basis; 7 (5.9%) were taking an H2 antagonist as needed. These frequencies of usage were not significantly different from those at baseline (12% and 8.3%, respectively). The proportion of patients with a 50% or greater reduction in PPI dose at 12 months who were, in addition, taking neither antacid or an H2 antagonist was 70%: CI[58%, 75%] by per protocol analysis.

Among the postapproval study participants, the treatment response rate at 24 months was 72% and the rate of cessation of PPI usage was 67% (Table 2). The Kaplan-Meier estimated fraction at 24 months was 65% on a time-to-first-failure basis (Fig. 1C). The corresponding estimate for cessation of PPI usage was 59% (Fig. 1D). When all treatment failures are taken into account, the 24-month estimate of 50% or greater reduction in PPI usage was 64%: CI[51%, 74%] and that of cessation of PPI usage was 56%: CI[44%, 67%].

GERD symptoms and quality of life

Improvement of GERD-HRQL symptoms (score \leq 11) was achieved in 78%: CI[69%, 85%] of the 114 multicenter trial patients with available data at 12 months, of whom, 97% also were treatment responders. The GERD-HRQL heartburn score improved by a median of 71%: CI[62%, 78%]. The corresponding median regurgitation score improvement was 77%: CI[72%, 86%]. The median physical component SF-36 questionnaire score was significantly improved by 12%: CI[7.4%, 17%]. The mental

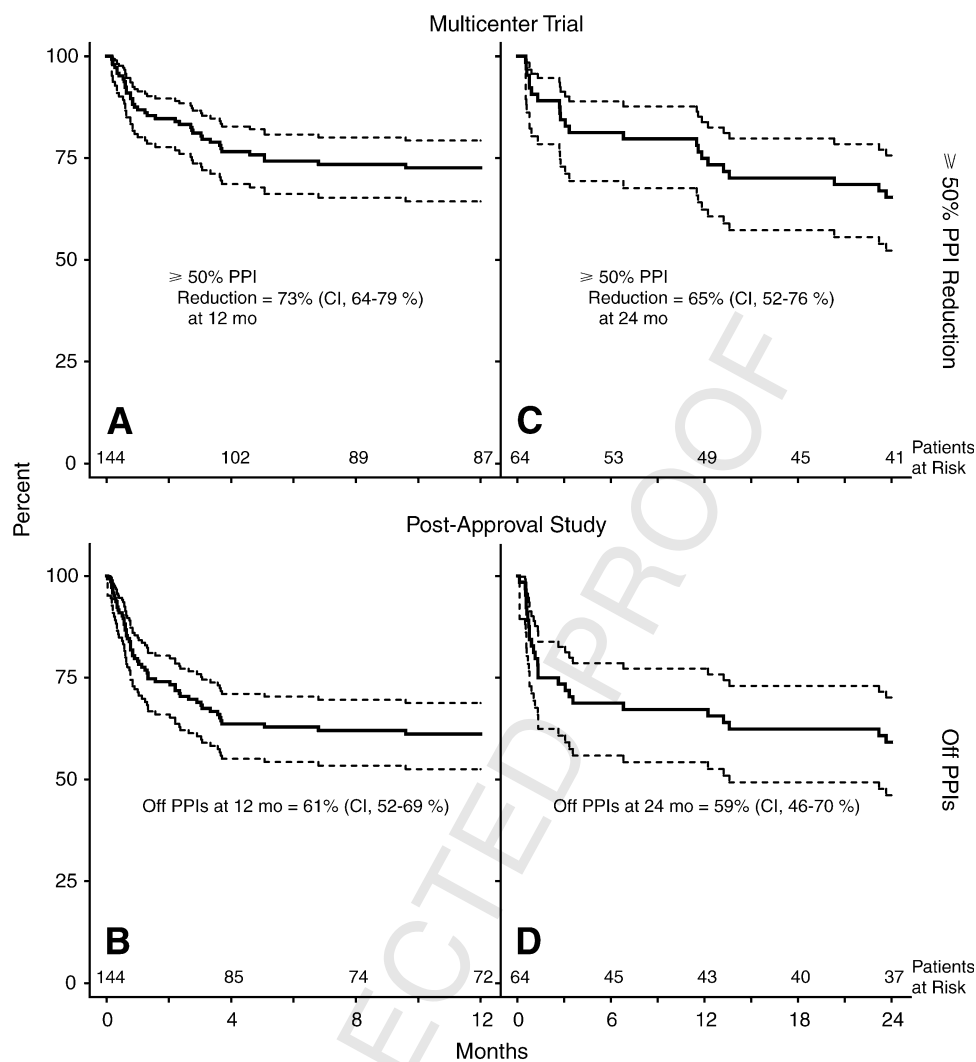


Figure 1. **A**, Kaplan-Meier estimated fractions of 50% or greater reduction in PPI usage (time-to-first-failure basis) to 12 months in multicenter trial. **B**, Kaplan-Meier estimated fractions of cessation of PPI usage (time-to-first-failure basis) to 12 months in multicenter trial. **C**, Kaplan-Meier estimated fractions of 50% or greater reduction in PPI usage (time-to-first-failure basis) at 24 months in postapproval study. **D**, Kaplan-Meier estimated fractions of cessation of PPI usage (time-to-first-failure basis) to 24 months in postapproval study. Dashed lines indicate CI (all 95% CIs).

component did not change significantly (median improvement 1.6%: CI[-0.8%, 4.0%]).

In the postapproval study, GERD-HRQL symptom scores improved promptly and significantly after implantation and remained stable thereafter. There was no evidence of temporal drift in either the GERD-HRQL heartburn score ($p = 0.4$) or the regurgitation score ($p = 0.3$) from 1 month through 24 months. At 24 months, the heartburn score was improved by a median of 80%: CI[71%, 87%] compared with baseline while not taking PPI. The median regurgitation score improvement was 88%: CI[79%, 92%]. The median heartburn score improvement at 24 months among patients who responded to treatment (88%: CI[81%, 93%]) was significantly greater ($p < 0.01$) than that of nonresponders (57%: CI[40%, 74%]). No significant difference was evident ($p = 0.2$) in the 24-month regurgitation score improve-

ment between responders (90%: CI[83%, 94%]) and nonresponders (71%: CI[56%, 92%]).

Esophageal manometry and pH monitoring

Paired baseline and 12-month esophageal manometry and ambulatory pH data were captured for 102 patients. There was no significant difference in the treatment response between patients who did and did not undergo pH monitoring at 12 months. Esophageal manometry revealed no significant change in LES pressure, length, or relaxation, or in peristaltic amplitude at 12 months. Extended esophageal pH monitoring was performed for a mean of 20 (3.3) hours at baseline and 20 (3.7) hours at 12 months. Esophageal acid exposure declined significantly at 12 months compared with baseline while not taking a PPI (Table 3, Fig. 2). Compared with baseline values, median supine, upright, and total times at pH less

TABLE 3. Data for pH monitoring in multicenter trial

Category	Baseline off PPIs			12 mo			p
	n*	Median	IQR	n*	Median	IQR	
Time at pH < 4 (%)							
Supine	93	7.1	1.0-17	93	2.1	0.0-9.0	<0.01
Upright	92	12	8.0-18	92	6.4	4.0-13	<0.01
Total	102	10	7.0-18	102	6.4	3.0-13	<0.01
No. episodes per 24 h	102	114	75-171	102	81	49-124	<0.01
Longest episode (min)	100	21	10-42	100	15	5.0-31	<0.01

PPI, Proton pump inhibitors; IQR, interquartile range.

*No. patients with available matched data at baseline and 12 mo for each of the indicated measurements.

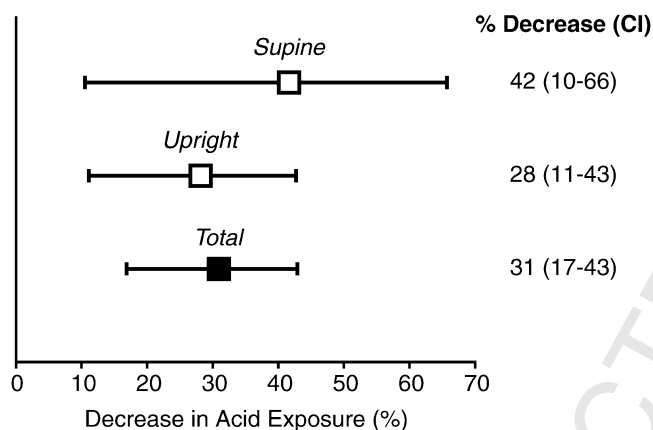


Figure 2. Median relative percent decreases between 12 months and baseline in supine, upright, and total percent time of esophageal exposure to pH < 4. Error bars depict exact CI. Absence of zero from CI (all 95% CI) indicates statistical significance (uncorrected for multiple testing).

than 4 decreased by 42%, 28%, and 31%, respectively (Fig. 2). Normalization of esophageal pH (total <5% at pH < 4) was achieved in 37%; CI[28%, 47%] of evaluable patients. The number of acid exposure episodes and their longest duration also were diminished at 12 months (Table 3).

Outcome predictors

An analysis of potential outcome predictors was undertaken for the multicenter trial that included patient demographic information, disease state, and history of prior treatment and implantation procedure-related outcome predictors. The following were specifically evaluated: age, gender, BMI, baseline assessments of hiatus hernia, esophagitis, symptoms while not taking a PPI, esophageal acid exposure, baseline PPI dose, duration of prior PPI therapy, study center, investigator, prior experience in

performing the Enteryx procedure, implantation volume in patients who underwent a single Enteryx procedure, implant shape (bleb, arc, or ring), and residual implant volume. There was no variable that reliably predicted outcome. Among patients with greater residual implant volumes, there was a tendency toward improved response, but this difference did not achieve statistical significance (p = 0.07, data not shown).

Esophagitis

Matched endoscopic observations consisting of baseline (while taking PPI) and 12-month follow-up were available for 107 patients. At baseline, erosive esophagitis was present in 32 patients (30%) (Grade I, n = 21; Grade II, n = 11). At 12 months after implantation, the grade of esophagitis was unchanged in 59 (55%), decreased in 14 (13%), and increased in 34 (32%). Of 11 patients with grade II esophagitis at baseline, 6 (54%) exhibited an improvement in grade at 12 months; in 8 of 21 patients (38%) with grade I esophagitis at baseline, the esophagitis was healed at 12 months' follow-up.

An increase in the severity of esophagitis was noted in 34 of the 107 patients (32%). In 19 patients (18%), the grade increased by one level; in 14 patients (13%), it increased by two levels; and, in a single patient, the grade of esophagitis progressed from 0 to III. This patient reduced PPI usage by 50% or greater at 12 months, experienced an improvement in GERD symptom score and a reduction in total acid exposure from 26% to 8%, and also had the highest baseline PPI use among all patients. Of 96 patients with a baseline esophagitis grade of 0/I, 26% developed grade II esophagitis at 12 months. The risk of progression from grade 0/I to grade II was significantly lower in treatment responders (relative risk, 0.28; CI[0.16, 0.67]) and in patients with a GERD-HRQL score of 11 or less at 12 months (relative risk, 0.35; CI[0.19, 0.76]).

Adverse events

In the multicenter trial, all implantation-related adverse events occurred during the initial 6 months of follow-up and resolved without long-term sequelae. At least one adverse event occurred in each of the 144 patients. None was considered potentially life threatening, and none necessitated surgical intervention. The most common adverse event was transient retrosternal chest pain (85% of patients). Prescription pain medications (e.g., propoxyphene, hydrocodone) were used routinely to manage the pain, which resolved within 14 days in 84% of affected patients. Mild to moderate dysphagia was encountered by 24% of patients at a median onset time of 6 days (range 1-17 days) after implantation. The types and the frequencies of adverse events observed after reimplantation were similar to those noted after the primary implant procedure (data not shown). There was no case of ulceration or extrusion of the Enteryx copolymer. Two patients in the multicenter trial and one enrolled in the postapproval study underwent esophageal dilation after Enteryx implantation. In all 3 cases, the dysphagia was considered moderate in severity by the investigator, and the dysphagia was resolved by the dilation. One patient experienced persistent dysphagia and was hospitalized on the 6th week after implantation. Evaluation demonstrated a paraesophageal collection that resolved completely with intravenous administration of antibiotics. In the postapproval study, there was no implantation-related adverse event between months 12 and 24 after implantation.

DISCUSSION

The preapproval clinical evaluation of Enteryx consisted of the present multicenter trial (reported in this article), as well as a second multicenter trial involving 93 patients in 6 European countries that had a nearly identical design.⁹ The present study expanded results for all 144 patients studied under the multicenter trial protocol and evaluated the durability of Enteryx implantation through 24 months. Most patients reduced or eliminated usage of PPI and experienced symptom relief. A significant reduction in esophageal acid exposure also was demonstrated. The interim 24-month data, which are based on the most extensive long-term follow-up reported thus far for any endoluminal GERD therapy, provide evidence of the durability of Enteryx implantation. The reduction or the elimination of PPI usage persisted in most patients, and the temporal pattern of symptom scores was remarkably stable.

Qualitatively, the novelty of the present study clearly rests in the 24-month data, which double the previously available span of follow-up by which the durability of Enteryx implantation may be judged. These data support current clinical decision making pending the completion

of the planned 36-month observation period. In addition, the 12-month results are described in a study population 69% larger than that in previous reports of the multicenter clinical trial in the United States.^{1,4} Consequently, it is possible to provide estimates of effectiveness and safety through 12 months that are more quantitatively precise.

The feasibility of relieving symptoms of GERD by augmenting the bulk of the distal esophagus was first recognized in the 1980s, but the durability of the effect was limited.¹⁰ After endoscopic injection of cross-linked bovine dermal collagen into the distal esophagus, for example, subjective and objective measures of reflux improved, but this response was only maintained for 6 to 9 months.¹¹ Injection of polytetrafluoro-ethylene into the LES also proved to be effective, albeit transiently.¹² In contrast to the superficial injection of these bulking agents, Enteryx is implanted into the muscularis propria and remains stable at this site for at least 24 months. The stability of the Enteryx implant within the cardioesophageal junction supports our belief that this procedure will remain effective over time.

Worldwide experience with implantation of Enteryx encompasses approximately 2600 procedures, and additional studies are ongoing. In the multicenter study of 93 patients in Europe, a PPI dosage reduction of 50% or greater was attained in 86% of patients at 12 months and cessation of PPI usage was attained by 65%. Symptoms and quality of life also were improved significantly.⁹

Durability is an important feature of any mechanical treatment for GERD. Several preliminary observations support the interim postapproval study findings and suggest that the beneficial effects of Enteryx are durable and sustainable. In a preliminarily reported study that included 8 patients followed for 3 years, significant residual implant was detected by spiral CT in 6 of the 8 patients.¹³ In another study, the implant volume remained stable at 80% of baseline through 12 months' follow-up among patients considered to be treatment responders, whereas the average implant volume was reduced to 40% of baseline among nonresponders.¹⁴ These observations support our belief in the durability of this procedure and its ability to provide prolonged therapeutic effect.

Any comparison of the results of Enteryx implantation with those of antireflux surgery or pharmacotherapy with PPI is complicated by several factors, including differing patient populations and outcome measures. Surgery often is reserved for patients with severe or refractory GERD, whereas the present study involved patients with PPI-responsive GERD of varying severity. Moreover, treatment responses can differ depending upon the patient population. For example, it has been shown that PPI-responsive patients have significantly greater symptom improvement after laparoscopic Nissen fundoplication than patients with refractory GERD.¹⁵ Among PPI-responsive patients undergoing laparoscopic Nissen fundoplication, one study found that mean symptom

improvement remained stable from 6 months through 24 months after surgery.¹⁵

The long-term risk of symptom relapse after open Nissen fundoplication varies widely, ranging from 15% to 62%.^{16,17} Similarly, there is wide variation in the outcome of laparoscopic Nissen fundoplication. In a study of 171 patients followed for a mean of 6.4 years, Bammer et al.¹⁸ found that 14% were being treated continuously with a PPI. In another study that included mostly patients with PPI-refractory GERD, 12% were using antisecretory medication for recurrence of heartburn or dyspepsia at 5 years after laparoscopic Nissen fundoplication.¹⁹ In a community-based experience, Vakil et al.²⁰ noted that 32% of patients were taking medications to counteract heartburn on a regular basis at a mean of 20 months after laparoscopic fundoplication.

Therapy with a PPI also may be associated with symptom relapse. In a randomized study, Lundell et al.²¹ compared continuous long-term PPI therapy with open antireflux surgery. After 5 years of follow-up, the point prevalence of moderate to severe heartburn was 16% in the PPI-treated group compared with 6% in the surgically treated group. In another randomized trial of long-term PPI maintenance therapy for 5 years in 243 patients with GERD, 5% to 7% were experiencing moderate or severe heartburn symptoms at the end of the study.²²

The precise role for Enteryx implantation in the treatment of patients with GERD remains to be determined. An effective endoluminal treatment would be an appealing option for patients with PPI-dependent GERD. The results of the open-label trials of Enteryx are promising, but more research with this technology is necessary. Enteryx effectively controls heartburn and regurgitation. Beyond this, Enteryx implantation potentially may benefit patients with an incomplete response to PPI, or it may have value as a salvage therapy for patients in whom surgery or other endoluminal modalities are unsuccessful. In a series of 11 patients with biliary reflux after gastrectomy followed for a mean of 18 months after Enteryx implantation, significant improvement in heartburn and regurgitation scores were noted.²³ The implantation procedure was well tolerated by patients, although two required a single endoscopic dilation for dysphagia. No long-term adverse sequelae were reported. At the present time, however, it is recommended that treatment with Enteryx be reserved for patients with PPI-responsive GERD symptoms.

In conclusion, the report encompasses a large cohort of patients with PPI-dependent GERD treated with Enteryx implantation into the distal esophagus. The findings indicate that Enteryx is a safe, effective, and durable endoluminal therapy for the majority of treated patients. Follow-up of this study population is ongoing, together with postapproval surveillance and a sham trial. The sham trial is a randomized investigation that addresses the extent to which the observed benefits are specifically

attributable to Enteryx implantation as opposed to a non-specific placebo response.

DISCLOSURES

Two authors (D.A.J. and G.B.H.) are consultants to Boston Scientific Corp.

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