

Endoscopic Mucosal Resection Useful for Barrett's

BY ALICIA AULT

Associate Editor, Practice Trends

WASHINGTON — Endoscopic mucosal resection seems to be safe and effective for Barrett's esophagus with high-grade dysplasia or intramucosal adenocarcinoma, and may help patients avoid an esophagectomy, according to a small study presented at a symposium sponsored by the Society of Surgical Oncology.

The procedure has been used to re-

move focal dysplastic lesions arising in Barrett's endothelium. Although that is successful initially, over time the rates of recurrence increase significantly, said Dr. Andrew Ross of the University of Chicago. This is not surprising, because most Barrett's dysplasias are microscopic and multifocal, so removing just a single focus probably is not very effective, he said.

Clinicians in Europe have shifted to using esophageal mucosal resection (EMR) to completely remove entire segments of Bar-

rett's esophagus, resulting in high remission rates out to 18 months, Dr. Ross said.

Aiming to replicate the European results, he and his colleagues reviewed a

See Point/Counterpoint on page 15.

prospectively collected database on all patients undergoing EMR for high-grade dysplasia (HGD) or intramucosal adenocarcinoma (IA) at the University of Chicago over a 5-year period.

There were 46 procedures in 26 patients (21 men and 5 women), with a median age of 65.5 years. Of these patients, 15 had HGD, 8 had IA, and 3 had a combination of the two. Half of the patients had short-segment and half had long-segment Barrett's. The median length in the long-segment Barrett's was 5.1 cm.

All patients underwent endoscopic ultrasound to rule out adenopathy and submucosal invasion. The EMRs were performed with a single-channel upper endoscope, but the surgical techniques evolved over time. Argon plasma coagulation was applied to resection margins. Surveillance endoscopy with a 4-quadrant biopsy every 1-2 cm was performed at 6-month intervals. All patients were maintained on twice-daily proton pump inhibitors.

Of the 26 patients, 16 have completed the protocol so far; 8 are awaiting the first follow-up endoscopy. There has been complete eradication—defined as normal-appearing squamous epithelium in surveillance endoscopy—in 11 patients who have been followed for a mean of 16 months. Two patients had residual HGD or IA, two had residual Barrett's with low-grade dysplasia, and one had residual Barrett's alone.

One patient was removed from the study because a submucosal invasion was discovered after the first EMR, and another died of unrelated causes. Most of the patients went home right after the EMR session.

The primary complication thus far has been esophageal stricture, affecting 7 (30%) of the 26 patients. Most saw a resolution of any dysphasia after one or two sessions of balloon dilation, but two patients had to have 10 dilations, Dr. Ross

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Brief Summary: For complete details, please see full Prescribing Information.

INDICATIONS AND USAGE: BYETTA is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.

CONTRAINDICATIONS: BYETTA is contraindicated in patients with known hypersensitivity to exenatide or to any of the product components.

PRECAUTIONS: General—BYETTA is not a substitute for insulin in insulin-requiring patients. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Patients may develop anti-exenatide antibodies following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. Patients receiving BYETTA should be observed for signs and symptoms of hypersensitivity reactions. In a small proportion of patients, the formation of anti-exenatide antibodies at high titers could result in failure to achieve adequate improvement in glycemic control.

The concurrent use of BYETTA with insulin, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors has not been studied.

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min; see Pharmacokinetics, Special Populations). In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects.

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. Therefore, the use of BYETTA is not recommended in patients with severe gastrointestinal disease. The development of severe abdominal pain in a patient treated with BYETTA should be investigated because it may be a warning sign of a serious condition.

Hypoglycemia—In the 30-week controlled clinical trials with BYETTA, a hypoglycemia episode was recorded as an adverse event if the patient reported symptoms associated with hypoglycemia with an accompanying blood glucose <60 mg/dL or if symptoms were reported without an accompanying blood glucose measurement. When BYETTA was used in combination with metformin, no increase in the incidence of hypoglycemia was observed. In contrast, when BYETTA was used in combination with a sulfonylurea, the incidence of hypoglycemia was increased over that of placebo in combination with a sulfonylurea. Therefore, patients receiving BYETTA in combination with a sulfonylurea may have an increased risk of hypoglycemia (Table 1).

Table 1: Incidence (%) of Hypoglycemia* by Concomitant Antidiabetic Therapy

	BYETTA			BYETTA			BYETTA		
	Placebo BID	5 mcg BID	10 mcg BID	Placebo BID	5 mcg BID	10 mcg BID	Placebo BID	5 mcg BID	10 mcg BID
	With Metformin			With a Sulfonylurea			With MET/SFU		
N	113	110	113	123	125	129	247	245	241
Hypoglycemia	5.3%	4.5%	5.3%	3.3%	14.4%	35.7%	12.6%	19.2%	27.8%

* In three 30-week placebo-controlled clinical trials. BYETTA and placebo were administered before the morning and evening meals. Abbreviations: BID, twice daily; MET/SFU, metformin and a sulfonylurea.

Most episodes of hypoglycemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see DOSAGE AND ADMINISTRATION). When used as add-on to a thiazolidinedione, with or without metformin, the incidence of symptomatic mild to moderate hypoglycemia with BYETTA was 11% compared to 7% with placebo.

BYETTA did not alter the counter-regulatory hormone responses to insulin-induced hypoglycemia in a randomized, double-blind, controlled study in healthy subjects.

Information for Patients—Patients should be informed of the potential risks of BYETTA. Patients should also be fully informed about self-management practices, including the importance of proper storage of BYETTA, injection technique, timing of dosage of BYETTA as well as concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised to inform their physicians if they are pregnant or intend to become pregnant.

The risk of hypoglycemia is increased when BYETTA is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea (see PRECAUTIONS, Hypoglycemia).

Patients should be advised that treatment with BYETTA may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen due to such effects. Treatment with BYETTA may also result in nausea (see ADVERSE REACTIONS).

Drug Interactions—The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 h before BYETTA injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when BYETTA is not administered. The effect of BYETTA on the absorption and effectiveness of oral contraceptives has not been characterized.

Warfarin: Since market introduction there have been some spontaneously reported cases of increased INR with concomitant use of warfarin and BYETTA, sometimes associated with bleeding.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 104-week carcinogenicity study was conducted in male and female rats and benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 mcg/day.

In a 104-week carcinogenicity study in mice, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 95 times the human exposure resulting from the maximum recommended dose of 20 mcg/day.

Exenatide was not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells.

Pregnancy—Pregnancy Category C—Exenatide has been shown to cause reduced fetal and neonatal growth, and skeletal effects in mice at systemic exposures 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day. Exenatide has been shown to cause skeletal effects in rabbits at systemic exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day. There are no adequate and well-controlled studies in pregnant women. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant mice an increased number of neonatal deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day.

Nursing Mothers—It is not known whether exenatide is excreted in human milk. Caution should be exercised when BYETTA is administered to a nursing woman.

Pediatric Use—Safety and effectiveness of BYETTA have not been established in pediatric patients.

Geriatric Use—BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients.

ADVERSE REACTIONS: Use with metformin and/or a sulfonylurea—In the three 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, adverse events with an incidence $\geq 5\%$ (excluding hypoglycemia; see Table 1) that occurred more frequently in patients treated with BYETTA (N = 963) vs placebo (N = 483) were: nausea (44% vs 18%), vomiting (13% vs 4%), diarrhea (13% vs 6%), feeling jittery (9% vs 4%), dizziness (9% vs 6%), headache (9% vs 6%), and dyspepsia (6% vs 3%).

The adverse events associated with BYETTA generally were mild to moderate in intensity. The most frequently reported adverse event, mild to moderate nausea, occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Adverse events reported in ≥ 1.0 to <5.0% of patients receiving BYETTA and reported more frequently than with placebo included asthenia (mostly reported as weakness), decreased appetite, gastroesophageal reflux disease, and hyperhidrosis. Patients in the extension studies at 52 weeks experienced similar types of adverse events observed in the 30-week controlled trials.

The incidence of withdrawal due to adverse events was 7% for BYETTA-treated patients and 3% for placebo-treated patients. The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and 0% due to vomiting.

Use with a thiazolidinedione—In the 16-week placebo-controlled study of BYETTA add-on to a thiazolidinedione, with or without metformin, the incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with metformin and/or a sulfonylurea. No serious adverse events were reported in the placebo arm. Two serious adverse events, namely chest pain (leading to withdrawal) and chronic hypersensitivity pneumonitis, were reported in the BYETTA arm.

The incidence of withdrawal due to adverse events was 16% (19/121) for BYETTA-treated patients and 2% (2/112) for placebo-treated patients. The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, <1% withdrew due to nausea. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of anti-exenatide antibody.

Spontaneous Data—Since market introduction of BYETTA, the following additional adverse reactions have been reported. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **General:** injection-site reactions; dysgeusia; somnolence, INR increased with concomitant warfarin use (some reports associated with bleeding). **Allergy/Hypersensitivity:** generalized pruritus and/or urticaria, macular or papular rash, angioedema; rare reports of anaphylactic reaction. **Gastrointestinal:** nausea, vomiting, and/or diarrhea resulting in dehydration with some reports associated with increased serum creatinine/acute renal failure that may be reversible if treated appropriately; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis.

Immunogenicity—Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with BYETTA.

OVERDOSAGE: Effects of an overdose include severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION: BYETTA therapy should be initiated at 5 mcg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). BYETTA should not be administered after a meal. Based on clinical response, the dose of BYETTA can be increased to 10 mcg twice daily after 1 month of therapy. Each dose should be administered as a SC injection in the thigh, abdomen, or upper arm.

Rx ONLY

Manufactured by Amylin Pharmaceuticals, Inc., San Diego, CA 92121
Marketed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company
1-800-868-1190

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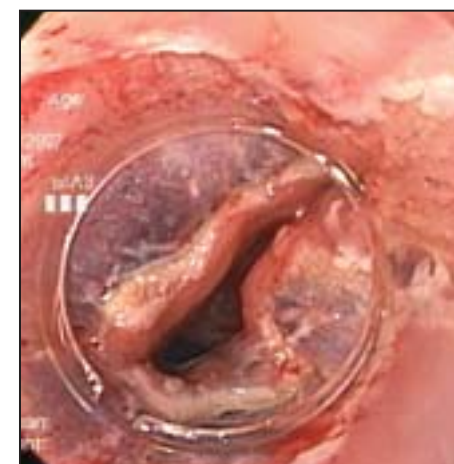
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Barrett's esophagus with high-grade dysplasia is shown before the procedure.



The same lesion is shown immediately after endoscopic mucosal resection.

PHOTOS COURTESY DR. ANDREW ROSS

Three Biomarkers Tied to Esophageal Ca Risk

BY ROBERT FINN
San Francisco Bureau

LOS ANGELES — A combination of three biomarkers may reliably predict which patients with Barrett's esophagus will progress to esophageal adenocarcinoma, Dr. Patricia L. Blount reported at the annual meeting of the American Association for Cancer Research.

In a study involving 243 patients with Barrett's esophagus, 79.1% of patients who had all three genetic abnormalities on baseline endoscopic biopsy progressed to esophageal adenocarcinoma within 6 years. Conversely, among patients who had none of the abnormalities, there was not a single progression to cancer in almost 8 years. Progression rates for patients with one and two abnormalities were 5.7% and 28.4%, respectively, at 6 years.

Compared with patients with no abnormalities, patients with any two of the abnormalities were 9 times more likely to progress to esophageal adenocarcinoma, and those with all three of the abnormalities were 39 times more likely to progress during an average follow-up of 71 months;

Continued from previous page

said. The strictures are probably occurring because the endoscopists found it more effective to do the total resection in one session—thus eliminating the scar tissue that resulted from doing the procedure in two sessions. Resection results are better, but strictures have increased.

Dr. Ross and his colleagues were also able to compare pre-EMR and post-EMR histopathology. The EMR removes large tissue specimens. There was histopathologic concordance in 70% of cases, but two patients were upstaged and six were downstaged according to the post-EMR histopathology, he said.

"It's a little bit concerning in that we rely heavily as endoscopists on the pinch biopsy specimens in the management, treatment, work-up, etc., of patients with Barrett's," Dr. Ross said.

Post-EMR histopathology revealed that HGD and IA were buried under normal-appearing squamous epithelium in nine patients, he said. "If you're doing surveillance endoscopy and you biopsied normal-appearing tissue, you may have missed cancerous lesions beneath the mucosa."

Compared with the standard biopsy protocol, EMR appears to provide more accurate histopathologic diagnosis and tumor staging, and it is a safe and effective alternative for eradicating HGD and IA in Barrett's, Dr. Ross said.

Stricture formation is a risk, especially with longer segments, he said.

"These preliminary data are encouraging," he said, adding that larger studies with longer follow-up are needed before widespread adoption of the technique.

He also noted the need for technological advances. "This is a difficult procedure to perform because our instruments are rudimentary and difficult to utilize."

Dr. Ross has no conflict of interests to disclose. ■

these differences were statistically significant. Patients with one abnormality were 1.8 times more likely to progress than those with no abnormalities, but this was not a significant difference.

In general, only about 10% of patients with Barrett's esophagus progress to esophageal adenocarcinoma, noted Dr. Blount, of the Fred Hutchinson Cancer Research Center, Seattle. Even frequent endoscopic surveillance can miss the small, focal lesions signaling progression to can-

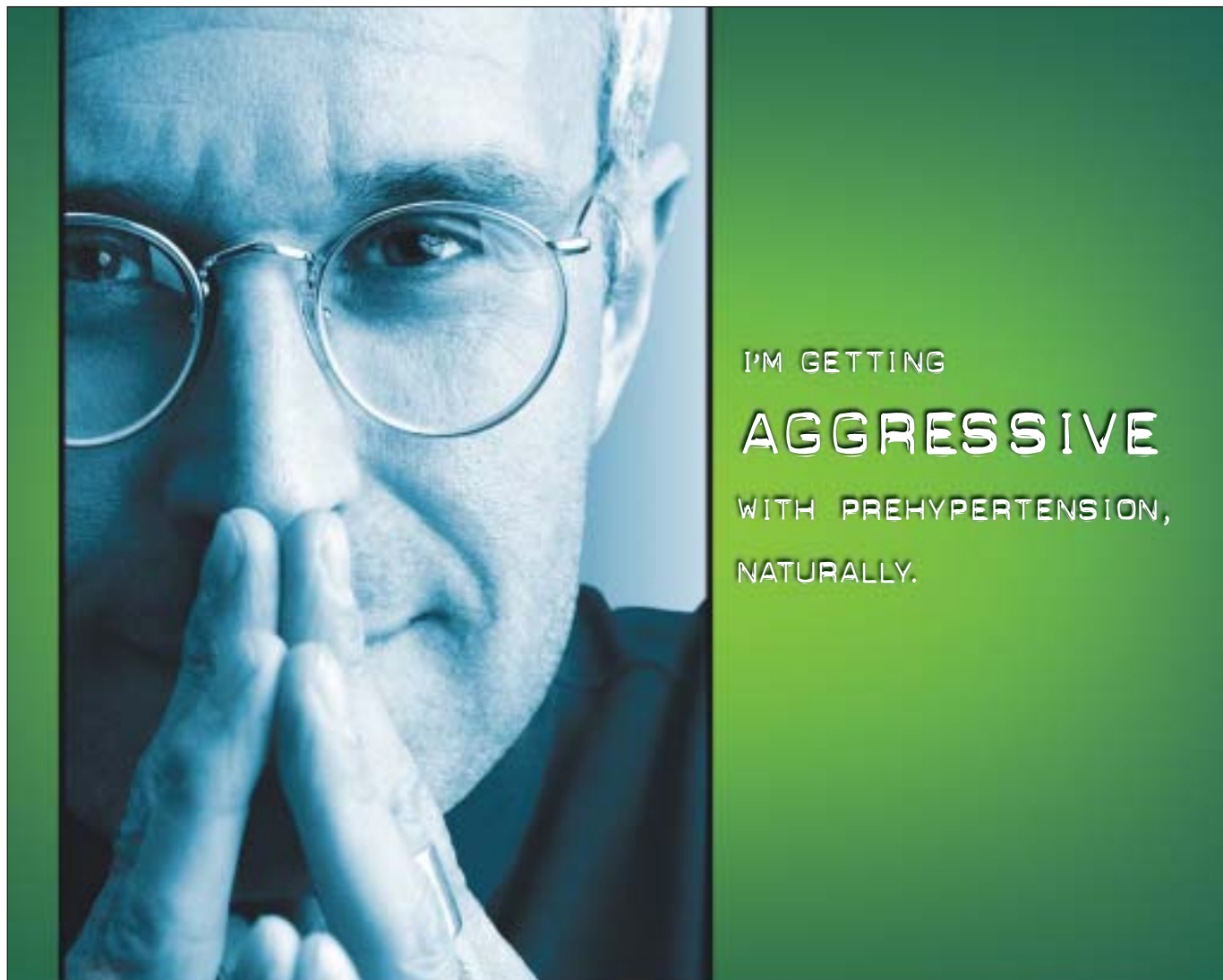
cer. Thus, a reliable method of predicting progression could have far-reaching clinical effects. The investigators are working to translate this research into a practical test that does not require the facilities of a research laboratory, he said.

The investigators focused on DNA aneuploidy and tetraploidy and on alterations in the genes for the tumor-suppressor proteins TP53 and CDKN2A accompanied by a loss of heterozygosity (LOH) for those genes. Patients who had either aneuploidy

or tetraploidy, 17p LOH (loss of heterozygosity on the short arm of chromosome 17), or 9p LOH (similarly, on chromosome 9) were more likely to progress to cancer.

As in other studies, the results of this study suggested that the use of NSAIDs may be protective against progression to esophageal adenocarcinoma.

The study was funded by the National Institutes of Health. Dr. Blount said that she had no conflicts of interest to disclose regarding the study. ■



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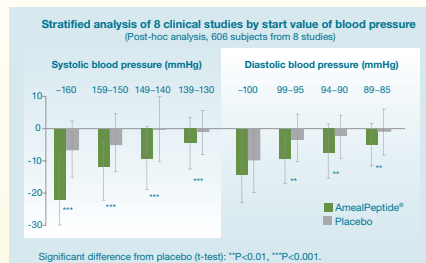


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