PPIs Become 'Addictive' For Some GERD Patients

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — Patients with gastroesophageal reflux disease are very difficult to wean off proton pump inhibitors, and there is evidence that patients essentially become "addicted" to acid suppression, findings of large study suggest.

Dr. Peter Bytzer of Copenhagen University and Køge (Denmark) Hospital, and Dr. Christina Reimer, also of the university, reported study findings that indicate proton pump inhibitors (PPIs) are nearly impossible to discontinue, even for patients who lack a formal indication for their use.

"We found that discontinuing long-term PPI therapy was possible in only a minority of patients and that the majority experiencing symptom relapse after discontinuing the drug had no abnormal endoscopic findings," Dr. Reimer said in a poster presentation. "Rapid recurrence of typical reflux symptoms was the main reason for restarting therapy, and 7 days of esomeprazole was helpful, despite the normal endoscopic findings."

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Major Finding: Of 76 patients who had unverified indications for a PPI, 11 were able to discontinue therapy without recurrence of symptoms during the 6 months of follow-up.

Data Source: A standardized search of patients prescribed PPIs by primary care physicians in the previous 12 months in Denmark.

Disclosures: Dr. Bytzer is a speaker or consultant for AstraZeneca Pharmaceuticals, Nycomed, and Orexo. Dr. Reimer has received grant support from and is a consultant to AstraZeneca Pharmaceuticals.

Dr. Bytzer and Dr. Reimer conducted a standardized search of patients prescribed PPIs by primary care physicians in the previous 12 months in Denmark. They identified 901 long-term users (at least 120 tablets), of whom 525 had an endoscopically verified diagnosis of esophagitis, Barrett's esophagus, or peptic stricture or had abnormal pH on monitoring, and therefore were categorized as having an indication for long-term treatment.

The remaining 376 patients were considered to have an unverified indication for a PPI and 76 of them agreed to attempt discontinue the drug. If symptoms recurred within 6 months after PPI withdrawal, patients underwent endoscopy. Those without abnormal findings were then randomized to 7 days of PPI therapy with esomeprazole 40 mg/day or placebo.

Of the 76 patients, 53 (63%) had symptom recurrence within the first week of discontinuing the PPI. The main symptoms were heartburn/acid regurgitation (48%) and dyspepsia (42%), Dr. Reimer reported at a DDW poster session.

On endoscopy, 31 (59%) had no abnormal findings.

Only 11 (14%) discontinued therapy without recurrence of symptoms during the 6 months of follow-up.

The 53 patients asked to restart therapy and were randomized to a PPI or placebo for 7 days; 80% of those taking esomeprazole had treatment success, compared with 13% receiving placebo.

Prescriptions for PPIs have essentially quadrupled in the past 10 years, according to data from the Danish Medicines Agency, Dr. Bytzer noted in a separate presentation at the meeting. "The increase in PPI use is explained by an increase long-term use."

This hypothesis is supported by evidence of an increased prevalence in acid-related conditions, more liberal prescribing habits—including empirical PPI therapy for unspecific dyspepsia—and PPI "dependency" as a result of acid rebound that requires more and more suppression, he said.

Ironically, studies have suggested that PPIs can actually stimulate acid secretion in healthy volunteers. In a 2007 systemic review, Hunfeld et al. concluded "there is evidence from uncontrolled trials for an increased capacity to secrete acid in [*Helicobacter pylori*]–negative subjects after 8 weeks of treatment" and "there is no strong evidence for a clinically relevant increased acid production after withdrawal of proton pump inhibitor therapy" (Aliment. Pharmacol. Ther. 2007;25: 39-46).

"In other words, once you remove the PPI you get an increased capacity to secrete acid. But is this clinically relevant? Will rebound acid hypersecretion lead to acid-related symptoms?" he questioned.

Apparently, it can. In a blinded withdrawal study conducted by Dr. Bytzer's group, 120 healthy volunteers were randomized to esomeprazole 40 mg or placebo for 8 weeks, after which the esomeprazole group crossed over to placebo for 4 weeks (Gastroenterol. 2009;137:80-7).

After crossing over, these patients experienced a significant increase in dyspepsia, heartburn, and regurgitation at weeks 10, 11, and 12.

These subjects had not had symptoms prior the study and were never on acid reducers. They were unaware of the shift to placebo. After the start of a PPI, gastrin significantly increased, and 44% got significant acid-related symptoms, he reported.

Other investigators have found increases in reflux laryngitis, heartburn, and dyspepsia after discontinuation of PPIs, he added.

To discontinue PPI therapy in long-term users, patients can slowly taper down doses over 3 weeks or so, he suggested, however, he said it remains difficult to discontinue PPI therapy, especially in patients with GERD. ■

Progress Made on Genetic Profile for Ulcerative Colitis

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — More than 50 genetic risk factors for ulcerative colitis have now been identified by the International Inflammatory Bowel Disease Genetics Consortium, said John D. Rioux, Ph.D.

"The work of the International IBD Consortium has dramatically increased the number of known UC [ulcerative colitis] loci and is expected to significantly increase our understanding of disease pathogenesis that relates to both shared and UC-specific inflammatory pathways," said Dr. Rioux of the University of Montreal. The Consortium spans 15 countries and employs over 80 clinical and basic researchers.

Genome-wide association (GWA) studies analyze "hundreds of thousands of genetic variants for thousands of patients and controls" to identify genetic risk factors, he said.

GWA studies have identified genetic risk factors for Crohn's disease.

While individual studies have been successful, the statistical power for gene discovery is limited by sample size.

The larger the sample size, the greater the number of genetic risk factors identified, he noted.

Previously, the Consortium performed one of the first studies to combine GWA results, and identified more than 30 risk factors for Crohn's disease.

"At that time, much less was known about the genetics of UC, with only the MHC and the IL23R gene having confirmed associations.

In the last year, multiple GWAs of UC have been done and have produced 18 independent new associations.

"These studies provided a unique opportunity to identify a much more complete catalog of genetic risk factors," he said.

In the current study, results from six GWA studies of UC were combined in a meta-analysis.

Data from 6,433 patients with UC and 20,999 population controls from North America and Europe were combined into a dataset.

"Out of nearly millions of polymorphisms examined," the tests ultimately revealed 75 independent genomic regions significantly associated with UC.

In preliminary investigations, the meta-analysis has confirmed 18 known UC loci, 21 novel loci, and 4 nominally significant loci (which investigators expect to become significant upon further analyses), for a total of 43 genetic risk factors to date.

Another 26 genetic risk factors are being studied but have not yet been replicated.

"Many of the UC genetic risk factors are shared with Crohn's disease—nearly 50%—as well as other inflammatory diseases," he noted.

The other inflammatory diseases include psoriasis, celiac disease, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and others.

"We predict there are at least 52 loci associated with UC, about 50% of which are shared with Crohn's disease and about 25% with other inflammatory diagnoses.

"The remainder appear to be UC-specific," he said.

"The research into the genetics of ulcerative colitis has highlighted the similarities and differences between ulcerative colitis and Crohn's disease, said Dr. María T. Abreu in an interview.

'We predict there are at least 52 loci associated with UC.'

DR. RIOUX

"It shows us some of the explanations for why patients with ulcerative colitis who have a *J*-pouch [also called an ileal pouch–anal anastomosis] may ultimately develop Crohn's disease," said Dr. Abreu, professor of medicine and chief, division of gastroenterology, University of Miami.

The Consortium is currently testing all novel loci in an independent set of 10,000 UC patients and a similar number of population controls to confirm these findings, but even the preliminary results provide "convincing evidence," he said, of associations to genes of biological significance to disease pathogenesis: TNFRSF14, JAK2, CARD9 and others.

An analysis of the literature suggests that novel UC genes pinpoint potential molecular mechanisms.

"In other words, each new UC gene contributes to the puzzle," he said.

For example, ETS1 on chromosome 11 has a profound impact on Th1 immune responses. DAP (death-associated protein) on chromosome 5 modulates mTOR (mammalian target of rapamycin) activity. WSB1 on chromosome 17 is a hedgehog-inducible ubiquitin ligase, and its loss results in spontaneous intestinal inflammation.

"We can begin to put these into biological pathways.

Many genes in these pathways protect or predispose to disease and we can identify novel targets and appropriate genetic testing within the context of clinical trials and patient selection," he said.

"Our work," he added, "has just begun." ■