PPIs Become ‘Addictive’ For Some GERD Patients

BY CAROLINE HELWICK
FROM THE ANNUAL DIGESTIVE DISEASE WEEK
NEW ORLEANS — Patients with gas-troesophageal reflux disease are very dif-ficult to treat with proton pump inhibitors, and there is evidence that patients essen-tially become “addicted” to acid suppress-ion, findings of large study suggest.

Dr. Peter Bytzer of Copenhagen Uni-versity and Rigshospitalet (Denmark) Hospital, and Dr. Christina Reimer, also of the uni-versity, reported study findings that indi-cate 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 major-ity 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.”

Dr. Bytzer and Dr. Reimer conducted a standardized search of patients pre-scribed PPIs by primary care physi-cians 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 pep-tic stricture or had abnormal pH on monitoring, and therefore were catego-rized as having an indication for long-term treatment.

The remaining 376 patients were con-sidered to have an unverified indication for a PPI and 76 of them agreed to at-tempt discontinue the drug. If symptoms recurred within 6 months of follow-up after the start of a PPI, these patients experienced symptom relapse after discontinuing treatment success compared with 13% receiving placebo.

Prescriptions for PPIs have essen-tially quadrupled in the past 10 years, accord-ing to data from the Danish Medicines Agency. Dr. Bytzer noted in a separate presentation at the meeting, “The in-crease in PPI use is explained by an in-crease in long-term use.”

This hypothesis is supported by evi-dence of an increased prevalence in acid-related conditions, more liberal pre-scribing habits—including empirical PPI use for unspecified dyspep-sa—and “PPI dependency” as a result of acid re-bound that requires more and more sup-pression, he said.

Ironically, studies have suggested that PPIs can actually stimulate acid secre-tion in healthy volunteers for a 2007 sys-tematic review, Hunfeld et al. concluded “there is evidence from uncontrolled trials for an increased capacity to se-crete acid in [Heliocobacter pylori]-negative subjects after 8 weeks of treatment” and ‘there is no strong evidence for a clinically relevant in-creased 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 ca-pacity to secrete acid. But is this clinically relevant? Will rebound acid hypersecre-tion lead to acid-related symptoms?’ he questioned.

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

After crossing over, these patients ex-perienced a significant increase in dys-pepsia, heartburn, and regurgitation at week 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 noted.

Other investigators have found in-creases 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 sug-gested, however, he said it remains dif-ficult to discontinue PPI therapy, espe-cially 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 Inter-national Inflammatory Bowel Disease Genetics Consortium, said John D. Rioux, Ph.D.

The work of the International IBD Consortium has dramatically in-creased the number of known UC [ul-cerative colitis] loci and is expected to significantly increase our understand-ing of disease pathogenesis that relates to both shared and UC-specific inflamma-tory 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 genotypes for thousands of patients and controls” to identify ge-netic 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 fac-tors identified, he noted.

Previously, the Consortium per-formed 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 con-firmed associations,” he said.

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 fac-tors,” 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 10,000 UC population controls from North America and Europe were com-bined into a dataset.

“Out of nearly millions of polymor-phisms examined,” the tests ultimate-ly revealed 73 independent genetic regions significantly associated with UC.

In preliminary investigations, the meta-analysis has confirmed 18 known UC loci, 21 novel loci, and 4 nominal-ly significant loci (which investigators expect to become significant upon fur-fher 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—near-ly 50%—as well as other inflammatory diseases,” he noted.

The other inflammatory diseases include, psoriasis, celiac disease, multiple sclerosis, systemic lupus erythe-matosus, 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 inflamma-tory 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. Marta T. Abreu in an inter-view.

“It shows us some of the explana-tions 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 num-ber of population controls to confirm these findings, but even the preliminary results provide “convincing evidence,” he said, of associations to genes of bio-logical significance to disease patho-genesis: TNRFSF14, 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 im-mune responses. DAP (death associ-ated protein) on chromosome 5 mod-u-lates mTOR (mammalian target of rapamycin) activity. WSB1 on chro-mosome 17 is a hedgehog-inducible ubiquitin ligase, and its loss results in spontaneous intestinal inflammation.

“We can begin to put these into bio-logical pathways.

Many genes in these pathways pro- tect or predispose to disease and we can identify novel targets and appropriate genes by testing within the context of clinical trials and patient selection,” he said.

“Our work,” he added, “has just begun.”