Current Challenges and Emerging Solutions in Upper GI Disorders: A Brief Report of the 2016 AGA Drug Development Conference

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In October 2016, the Center for Diagnostics and Therapeutics (CDT) of the American Gastroenterological Association (AGA) held its first Drug Development Conference. Over a 2-day period, researchers, clinicians, Food and Drug Administration (FDA) personnel, and representatives of the pharmaceutical industry and patient advocacy groups convened in Washington, DC, to discuss current unmet needs and future strategies in 4 disorders of the upper gastrointestinal (GI) tract. The 4 disorders discussed were gastroesophageal reflux disease (GERD), eosinophilic esophagitis, gastroparesis, and functional dyspepsia. Experts in these various disorders presented information on current and potential therapeutic strategies, issues of clinical trial design, and possible therapeutic endpoints to be adopted in future clinical trials. Panel discussions after each session included representatives from the FDA and the pharmaceutical industry.

Established in 2014, the CDT is the AGA's third specialty center. It joins the AGA Center for GI Innovation and Technology and the AGA Center for Microbiome Research and Education. The mission statement of the CDT is "To support the development of therapies and diagnostic tests that will enhance human health and improve the lives of patients with digestive disorders." The aim of the recent Drug Development Conference was to bring together the principal stakeholders (as outlined) to further the mission of the CDT as it pertains to upper GI disorders.

In this article, we aim to present a summary of the recent Drug Development Conference and to highlight some of the issues that were discussed. Further, more detailed information will be made available in 4 individual white papers that are currently being prepared by the participating faculty members. These papers will be submitted for publication to *Clinical Gastroenterology and Hepatology*.

Why Focus on Upper GI Tract Disorders?

Disorders of the upper GI tract are highly prevalent in specialized and primary care and constitute a large proportion of outpatient and hospital visits in the United States. Data from the AGA's Burden of Disease survey[1] found that, in 2009, there were >15 million outpatient visits for abdominal pain, almost 3 million each for problems with nausea or vomiting, almost 2 million for heartburn or "indigestion," and >1 million for dysphagia. Among the top 15 physician-made diagnoses for GI disorders in 2009 were GERD (ranked first with >8.8 million diagnoses), "gastroenteritis and dyspepsia" (ranked third with >4 million diagnoses), nausea and vomiting (ranked tenth with >1.6 million diagnoses), and dysphagia (ranked 15th with just >1 million diagnoses). Furthermore, the burden of upper GI tract disorders extends beyond the outpatient setting; during 2009, there were >65,000 hospital discharge diagnoses of reflux disease and >130,000 discharge diagnoses of functional/motility disorders. Discharge diagnoses of reflux disease had clearly diminished over the preceding 9 or 10 years. However, this decrease had been more than offset by a marked increase in the number of patients who had been hospitalized and found to have some functional GI or motility disorder. Among the latter group, there had been a 26% increase over the preceding 9–10 years. Those patients had a median duration of hospital stay of 4.0 days at an estimated cost of >$972 million. Among the patients with diagnoses of functional and/or motility disorders would have been many with gastroparesis and/or functional dyspepsia—or related functional GI disorders such as irritable bowel syndrome.

Upper GI Disorders Are Not All Acid Related

Proton pump inhibitors (PPIs) have been available since the early 1990s. The extensive, cumulative clinical experience with them justifies their use for patients with troublesome heartburn owing to GERD, and in patients at high risk of upper GI tract ulcers because of long-term use of nonsteroidal anti-inflammatory drugs and/or aspirin. However, there has been a tendency to prescribe or

Abbreviations used in this paper: AGA, American Gastroenterological Association; CDT, Center for Diagnostics and Therapeutics; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GI, gastrointestinal; PPI, proton pump inhibitor; PRO, patient-reported outcomes.

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recommend PPIs for patients with less specific symptoms or weaker indications. PPIs have been used frequently for patients with dyspeptic symptoms despite the observation from clinical trials and routine clinical practice that only a minority of patients show marked benefit. PPIs are also often recommended for a variety of symptoms thought to emanate from the upper GI tract, even when such symptoms (eg, upper abdominal fullness, bloating, early satiety, etc) would be unlikely to be acid mediated or helped by the pharmacologic suppression of gastric acid secretion. It is clear that better therapeutic options are required for specific disorders of the upper GI tract, including those discussed at the recent conference.

Haven't PPIs Solved the GERD Problem?

In the early 1990s, there was much optimism that this question might have been answered in the affirmative. At that time, patients with heartburn due to GERD often had a miserable time and were recommended to try a variety of (generally ineffective and non–evidence-based) lifestyle modifications along with liberal quantities of antacids and H_2-receptor antagonists. Our approach to those patients was simple then; we offered them an upgrade to PPI treatment and felt generally satisfied with the outcomes. After all, early and subsequent randomized, controlled trials consistently showed superiority of any PPI over any H_2-receptor antagonist in the healing of erosive esophagitis and in the control of heartburn in patients with eosinophilic esophagitis. So, problem solved—right?

Unfortunately, life is rarely that simple. For one thing, most patients with GERD do not have erosive esophagitis and—perhaps—our focus on endoscopic healing rates of erosive esophagitis was not appropriate. GERD patients often experience a variety of symptoms aside from heartburn and not all of these respond satisfactorily to PPI treatment. Many of the GERD patients whom we now see at our clinics are dissatisfied with PPI treatment and often complain of persistent heartburn and/or other symptoms such as regurgitation[2,3] and epigastric burning or discomfort. This in itself represents one of the recurring themes from the Drug Development Conference—namely, that of an overlap diagnosis. For example, patients with a firm diagnosis of GERD may have other symptoms that are troublesome to them. These symptoms may be sufficient to fulfill the diagnostic criteria for an additional disorder such as dyspepsia or irritable bowel syndrome. It is clear that patients' own assessments of treatment outcomes may be very different from those of their health care providers—hence, the growing importance of properly designed and validated patient-reported outcomes (PRO) measures for use in future clinical trials. (The issue of PRO measures was another recurring theme of the conference impinging on all 4 topic areas discussed.)

The forthcoming white paper on GERD will include future directions for the development of agents that can, perhaps, be added to PPI therapy and that might be suitable for GERD patients whose heartburn is well-controlled by a PPI but whose other symptoms are not. Regurgitation is the second most frequent symptom of GERD. It is clear that PPIs are much less effective for this complaint than they are for heartburn and that regurgitation is frequently responsible for apparent "failure" of PPI treatment in GERD.[2,3] Furthermore, persistent regurgitation has a major negative impact on patients' quality of life. Future clinical trials of such agents might focus more on improvement in regurgitation as a predefined primary endpoint. Again, the importance of properly validated PRO measures and their incorporation into any assessment of efficacy cannot be overemphasized. Although some recent trials of motility-modifying agents in GERD patients who had an incomplete response to PPI treatment failed to meet their primary endpoints this may have been due to lack of therapeutic efficacy, or to the inclusion into the trials of patients with the wrong symptom profile(s), or some combination of the two.

Eosinophilic Esophagitis—Where Allergy Meets Acid?

Eosinophilic esophagitis is a disorder of increasing importance. Long recognized by pediatricians, it is a relative novelty for adult gastroenterologists. The condition remains poorly understood and underappreciated by nonspecialists. It is often confused with GERD (with which it has overlap symptoms), and often goes undiagnosed and untreated for years. There has been debate and disagreement about whether eosinophilic esophagitis and GERD are distinct disorders or whether they form part of a broad spectrum of esophageal conditions. That concept may be better established in pediatric practice than it currently is in adult practice. Furthermore, there has been additional confusion concerning the emerging concept of PPI-responsive esophageal eosinophilia. Patients with PPI-responsive esophageal eosinophilia are currently indistinguishable from those with typical eosinophilic esophagitis on clinical, endoscopic, or histologic criteria. PPIs have traditionally been considered solely as acid-suppressing drugs. However, this may be an oversimplification; discussion at the conference included the possibility of some hitherto unrecognized anti-inflammatory properties of the PPIs. However, why these should be conveniently manifested in the esophagus is unclear. This seems to be a "watch this space" issue.

In clinical practice, patients are generally diagnosed with eosinophilic esophagitis when they have symptoms consistent with the diagnosis along with typical endoscopic findings and histologic confirmation of an abnormally high eosinophilic infiltrate on esophageal biopsies (currently defined as $\geq$15 eosinophils per high-power field). Distinction between PPI-responsive esophageal eosinophilia and "true" eosinophilic esophagitis is generally made on the response—or lack thereof—to a course of high-dose PPI treatment. However, it is unclear how best to follow those patients in clinical practice. Those who do not respond to PPIs—and who are currently considered to have eosinophilic esophagitis—can be managed with swallowed steroids or elimination diets or—when there is esophageal