The 71st Annual Scientific Meeting of the American College of Gastroenterology (ACG) was held in Las Vegas, Nevada. More than 1,000 abstracts were presented at the meeting. Luckily for our readers, Drs. Rex, Talley, Katz, Hanauer, and Sandborn were on hand to collect and present the latest information, and select the most important findings in their areas of expertise.

Colonoscopy and Colorectal Cancer Prevention

Bowel Preparation

The inability of the gastroenterological community to identify a bowel purgative for colonoscopy that maximizes the 3 criteria by which bowel preparation is judged (ie, effectiveness, safety, and tolerability) remains a major problem. Gastroenterologists know from experience that patients consider bowel preparation to be the least tolerable portion of the colonoscopy process. Data from the Clinical Outcomes Research Initiative in the United States\(^1\) and a European quality study\(^2\) have demonstrated that ineffective bowel preparation interferes with the detection of both small and large adenomas. At the ACG meeting, we saw a direct comparison of 2-L polyethylene glycol (PEG) plus bisacodyl, which is now widely used in the United States, with the 32-tablet regimen of sodium phosphate (OsmoPrep; Salix Pharmaceuticals, Morrisville, NC). The sodium phosphate regimen was significantly more effective than the PEG plus bisacodyl regimen, and more polyps were detected in the sodium phosphate arm (\(P = .041\))\(^3\) even though the procedure duration was shorter (14.2 vs 15.9 minutes; \(P = .01\)) with the sodium phosphate tablets. This was the first time an experimental study was used to show an association between better-quality bowel preparation and higher polyp detection rates. No data on adenoma detection were reported. Efficacy was scored on a 4-point scale (1 = excellent, 2 = good,
Report from the ACG continued

3 = fair, 4 = poor). Overall, bowel preparation with sodium phosphate tablets was superior (1.5 vs 1.8; P < .0001), and the tablets also showed superiority in the ascending colon (1.4 vs 1.8; P < .0001). Sodium phosphate tablets resulted in fewer adverse events (66% vs 82%; P = .0003), including less gastrointestinal discomfort, abdominal distention, abdominal pain, and vomiting.4

Recent reports of renal failure in patients with previously normal renal function who had received oral sodium phosphate solution (OSPS) or sodium phosphate tablets have raised considerable concern about the use of sodium phosphate as a bowel preparation for colonoscopy. The primary risk factors in clinical trials have included female gender and a history of hypertension. In the large numbers of clinical trials reported in the literature using OSPS and sodium phosphate tablets, there has never been a reported case of phosphate nephropathy and renal failure.

Reports at the ACG attempted to further understand the renal toxicity of sodium phosphate. A retrospective study of 230 patients who had received sodium phosphate preparation (n = 144) or PEG (n = 86) showed that 5.6% of patients developed a greater than 50% increase in their creatinine from baseline after colonoscopy.5 However, there was no difference between sodium phosphate and PEG in the proportion of patients who developed an elevation in their serum creatinine (5.6% vs 4.6%; P > .9). None of the patients had significant acute or chronic renal failure.

Another study examined weight, postural changes, and adverse events for 7 days before colonoscopy, the day of the procedure, and 48 to 72 hours after the procedure in 427 patients undergoing preparation with sodium phosphate compared with 432 patients undergoing preparation with PEG.7 Weight loss in the two groups was similar (sodium phosphate 2.1 ± 3.3 lb; PEG 2.4 ± 2.8 lb). This effect of PEG runs counter to the commonly held belief that patients receiving PEG are not at risk for dehydration. Postural hypotension developed in 3 patients receiving sodium phosphate and 4 patients receiving PEG.7 Although studies of this type are of considerable interest, they are insufficient to reassure us regarding the safety of sodium phosphate, as the incidence of renal failure after sodium phosphate is probably extremely low and would be quite difficult to identify in a prospective trial. Sodium phosphate is superior to PEG in both tolerability and effectiveness but probably inferior with regard to safety. Clinicians considering use of sodium phosphate should emphasize in their oral and written instructions to their patients the need for aggressive hydration before, during, and after bowel preparation with this agent. There is a strong rationale for believing that adequate hydration can prevent any renal toxicity associated with sodium phosphate, and in the only 5 cases of phosphate nephropathy reported in the literature in which the details of hydration were provided, the amount of hydration taken by the patients was clearly inadequate.5,8

Recent data have suggested that a low-residue diet taken for breakfast and even lunch on the day before colonoscopy is associated with equal or better quality of bowel preparation compared with clear liquids on the entire day before the procedure.

There is no longer any rationale for the use of Visicol (Salix Pharmaceuticals, Morrisville, NC), as the new OsmoPrep formulation of sodium phosphate tablets has achieved the goal of eliminating the microcrystalline cellulose filler that creates the white snowy substance seen in the colon when Visicol is used. In addition, the new sodium phosphate tablets are smaller, waxier, and easier to swallow and have been approved by the US Food and Drug Administration (FDA) at a reduced dosage of 32 tablets: 20 taken the evening before colonoscopy and 12 taken on the day of the procedure. This formulation represents a 20% reduction in the phosphate load compared with the standard 40-tablet Visicol regimen, and the manufacturer of OSPS has been interested in whether some reduction in OSPS dosage could still be effective. Previous work showed that two 30-mL doses of OSPS were inferior to two 45-mL doses. At the ACG, a randomized trial was reported comparing one 45-mL dose on the evening before
colonoscopy was as effective as a clear liquid diet when combined with 4 L of PEG. Willingness to repeat the procedure and tolerability were superior with the fiber-free diet.10

Sedation
The use of propofol by nonanesthesiologists remains controversial. Alternative approaches include the use of computer-assisted sedation and a propofol prodrug called fospropofol disodium (Aquavan injection; MGI Pharma, Bloomington, MN). The companies developing these products are targeting them for FDA approval for administration by nonanesthesiologists. Fospropofol is typically given in combination with a small preliminary dose of fentanyl. A randomized, controlled trial of 127 patients was reported comparing 2.0 mg/kg, 5.0 mg/kg, 6.5 mg/kg, and 8.0 mg/kg of fospropofol with midazolam 0.02 mg/kg, 6.5 mg/kg, and 8.0 mg/kg of propofol plus low-dose narcotic benzodiazepine regimen, sometimes called balanced propofol sedation, was less likely to produce deep sedation than were narcotics and benzodiazepines alone.

Capsule Colonoscopy
A long-term goal of Given Imaging Inc. (Duluth, GA) has been to develop a capsule colonoscopy. The technical problems with capsule colonoscopy are substantially greater than those with endoscopy of the esophagus and small bowel. The first human trials described at ACG. The device was a two-headed capsule with each end acquiring 2 frames per second and with a battery life of 10 hours. A series of laxatives and prokinetic agents were used to clean the colon and accelerate the capsule through the small bowel and colon. One study enrolled 90 patients, 84 of whom were fully evaluated. These patients had a mean age of 57 years and 36 were female. Capsule excretion, defined as passage into the toilet before the battery expired, occurred in 74% of the cases; in 16 cases, the capsule reached the rectosigmoid. Patients underwent conventional colonoscopy after completion of the capsule colonoscopy. Among the 20 patients (24%) who had either 1 polyp ≥6 mm or 3 or more polyps of any size, the capsule identified 14 (70%) and the standard colonoscopy identified 16 (80%). Of 45 patients in whom polyps of any size were found, 34 (76%) had polyps detected by the capsule colonoscopy and 36 (80%) had polyps detected by standard colonoscopy. There were no adverse events. In another study, 25 patients aged 50 and older underwent capsule colonoscopy, then within 3 weeks, but on a separate day, underwent same-day computed tomography (CT) colonography and conventional colonoscopy. Visualization of the entire colon was better, with the capsule exiting the rectum in 22 of 25 patients. The average time to expulsion was 4 hours. The same definitions for significant end points as those used in the prior study resulted in significant findings being identified in 7 of 11 patients by capsule colonoscopy, 6 of 11 by CT colonography, and 9 of 11 by blinded conventional colonoscopy. Additional, larger multicenter trials will begin in the near future.

CT Colonography
There is currently a vigorous debate over which polyps detected by CT colonography require colonoscopy and polypectomy. The ACG recommends that patients with polyps ≥6 mm or those with 3 polyps of any size should be offered polypectomy. Many radiologists no longer even report polyps ≤5 mm. Patients with polyps in the 6- to 9-mm range may be offered polypectomy or may undergo CT colonography “surveillance,” in which the test is repeated in a couple of years. The prevalence of high-grade dysplasia and cancer in adenomas <1 cm is of considerable importance in making decisions on these issues because the natural history of small polyps is really unknown. A single gastroenterologist from the United States in private

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have shown that more often than not, patients claim a preference for CT colonography over optical colonoscopy, even though they find CT colonography more painful because it is done without sedation. Previous studies of CT colonography have shown that more often than not, patients claim a preference for CT colonography over optical colonoscopy, even though they find CT colonography more painful because it is done without sedation.

The premier CT colonographer in the United States is Perry Pickhardt. At the ACG, they reported a study suggesting that patients who had only rectosigmoid polyps detected at CT colonography could undergo flexible sigmoidoscopy and polypectomy rather than colonoscopy. The investigators retrospectively identified 203 patients who had only rectosigmoid polyps identified by CT colonography. They found that only 3 of these patients (1.5%) had advanced neoplastic lesions during colonoscopy. The Bethesda group concluded that the miss rates of CT colonography followed by flexible sigmoidoscopy when CT colonography showed only rectosigmoid lesions were comparable to the miss rates for colonoscopy.

Two studies were reported on the performance of CT colonography for its most commonly used indications in the United States: for patients with incomplete colonoscopy and those with medical contraindications to conventional colonoscopy. In a study of patients with incomplete colonoscopy, those whose colon was poorly visualized at CT colonography had a lower yield of polyps compared with those whose colon was adequately visualized (7% vs 29%; P = .09). Overall, there were significant problems with nonvisualization of portions of the colon in this population. In a group of 31 patients undergoing CT colonography followed by conventional colonoscopy, it was found that 98% had at least one extracolonic finding. Very close observation and cost analysis were performed in the follow-up studies. Evaluation of extracolonic findings was performed in 24% of the patients. Subsequent imaging studies included 37 CT scans, 16 ultrasound studies, 6 magnetic resonance imaging (MRI) scans, 13 plain films, and...
The angle of view on the scopes (Olympus America Inc., Center Valley, PA). The angle of view colonoscopies, although the examination times for the second examinations were shorter than those for the first. This fascinating software may eventually be used to provide real-time feedback and global inspections. It is very promising to see continued progress toward our goal of having safe, comfortable, and highly effective colonoscopic withdrawal technique from digitized video files. This software evaluates factors such as the "clear withdrawal time," which refers to the duration of the withdrawal phase in which there are no out-of-focus frames. In addition, the software can analyze the number of back-and-forth movements and the fractions that have close inspection of the colonic wall or global inspections. This fascinating software may eventually be used to provide real-time quality assessments of colonoscopic withdrawal, which may be important in reducing the large variation among endoscopists in their ability to detect adenomas.

A new tandem colonoscopy study was performed using wide-angle, high-resolution Olympus colonoscopes (Olympus America Inc., Center Valley, PA). The angle of view on the colonoscopes was 170°. Patients were randomly assigned to undergo the first colonoscopy in either white light or narrow band imaging. A total of 118 patients participated; the overall miss rate for adenomas was 12%, compared with an overall miss rate of 24% in the largest previous tandem colonoscopy study. The examiners felt the differences were the result of the high-resolution, wide-angle colonoscopes, although the examination times for the second examinations were shorter than those for the first; this was accompanied by a trend toward lower adenoma detection with the wide-angle colonoscopes.

Narrow band imaging is a method of potentially improving adenoma detection. Microcapillaries on the surface of adenomas make them appear a darker brown, with a greater contrast in color between the adenoma and the surrounding normal mucosa compared with what is seen with white light. A randomized, controlled trial using high-definition colonoscopes in 434 subjects compared white light with narrow band imaging. The study found no difference in adenoma detection rates between the two arms, but the overall adenoma detection rates in both arms were extremely high—in fact, they were the highest ever reported. The overall prevalence rate of the adenomas was above 60%, and two thirds of the study population, for whom screening was indicated, had a prevalence of adenomas above 55%, by far the highest ever reported in a screening colonoscopy study. Given other data on wide-angle colonoscopy, the results suggest that high definition may significantly contribute to adenoma detection.

More information was presented on the NeoGuide colonoscope (NeoGuide Systems, Los Gatos, CA), which is a new platform for which commercialization is expected next year. The instrument consists of a series of links or bending sections. It is designed to prevent looping, and the instrument passes around curves in a snakelike fashion, with information about the shape of the curve successively transmitted back along the links comprising the scope. Additional features described at the ACG meeting include a mathematical representation of the shape of the scope, which is demonstrated on the monitor, and a joystick control head, a change from the typical 2-knob control head familiar to endoscopists.

A study from the Memphis Veterans Administration Hospital examined 1013 veterans who underwent at least 2 colonoscopies between January 1998 and April 2005. Fourteen patients developed colorectal cancer within 5 years of a colonoscopy to the cecum: 2 had large adenomas but refused surgery and 12 had apparent missed lesions. Eight of the 12 patients with apparent missed lesions had tumors proximal to the splenic flexure, and 8 of the 12 were stage 3 or 4 at presentation. A trainee was involved in only 4 of the 12 colonoscopies, and active colitis with acute lower gastrointestinal bleeding, the presence of solid stool, and a redundant colon may have contributed to missed diagnosis in 4 patients. Nine of the 12 patients had expired by April 2005.

Summary

It is very promising to see continued activity in colonoscopic research, and we continue to make incremental progress toward our goal of having safe, comfortable, and highly effective colonoscopies. More information was presented on the NeoGuide colonoscope (NeoGuide Systems, Los Gatos, CA), which is a new platform for which commercialization is expected next year. The instrument consists of a series of links or bending sections. It is designed to prevent looping, and the instrument passes around curves in a snakelike fashion, with information about the shape of the curve successively transmitted back along the links comprising the scope. Additional features described at the ACG meeting include a mathematical representation of the shape of the scope, which is demonstrated on the monitor, and a joystick control head, a change from the typical 2-knob control head familiar to endoscopists.

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colonoscopies performed on a widespread basis. 

[Douglas K. Rex, MD]

Functional Gastrointestinal Disorders

The following represent a selection of interesting and clinically relevant therapeutic presentations in functional GI disorders at ACG 2006.

Bacterial Overgrowth and Antibiotic Therapy in Irritable Bowel Syndrome

Following the recent publication in the Annals of Internal Medicine on the efficacy of rifaximin in irritable bowel syndrome (IBS), there remains intense interest in whether such an approach should be more widely considered. This is still controversial, and further data presented at this year’s ACG meeting, although providing some additional clarification, indicate there are still many more questions than answers.

There is accumulating evidence that antibiotic therapy may provide some benefit in IBS, but this is not necessarily attributable to bacterial overgrowth in the small intestine. For example, Ruff and colleagues reported their experience with patients who underwent duodenal aspirates for bacterial overgrowth. Nearly three quarters of these patients reported bloating. However, there was no association between IBS or bloating and small bowel bacterial overgrowth in this patient cohort. In a plenary presentation from Northwestern University, 175 patients with IBS and 23 controls were evaluated by lactulose hydrogen breath testing. There was no increase in abnormal hydrogen breath tests for bacterial overgrowth in IBS compared with controls. However, there was an association between methane production and constipation in the IBS patient group, which is consistent with other results published elsewhere. On the other hand, the group from Cedars-Sinai reported their experience in terms of a retrospective chart review of 84 patients with Rome I criteria for IBS who were treated with rifaximin. Of those who clinically responded to rifaximin, 81% had a normal follow-up breath test, whereas only 16% of non-responders had a normal follow-up breath test. However, the number of patients in this study was relatively small and highly selected, and this was not a controlled study.

Based on the available evidence, it seems reasonable to conclude that there is a group of patients with IBS who will respond to antibiotic therapy, at least in the short term. The published data further suggest that bloating, in particular, can improve. Notably, about two thirds of patients, at least in the randomized controlled studies, do not respond, although better results have been reported in the uncontrolled studies (probably reflecting bias rather than truth).

New Approaches to Chronic Constipation

Opioid receptor antagonists are a class of drugs of particular interest in chronic constipation. In opioid-induced constipation, one would expect opioid receptor antagonists to be potentially beneficial. This has been shown for alvimopan, a mu-opioid receptor antagonist. However, whether this drug class is efficacious in non-opioid chronic constipation is not known. Kelleher and colleagues presented the results of a randomized, double-blind, placebo-controlled study of alvimopan in different doses in chronic constipation. They looked at the change in mean spontaneous complete bowel movements at 4 weeks. They found that during 1 to 4 weeks, there were no significant differences in mean weekly spontaneous complete bowel movements between any of the doses of alvimopan used and placebo. Hence, it does not appear likely that this approach will prove clinically useful in chronic idiopathic constipation, in contrast to opioid-induced constipation. More work, however, is needed to confirm these observations.

Lubiprostone is a chloride channel activator that induces intestinal fluid secretion. The drug has been approved for chronic constipation therapy based on short-term clinical trials. In an open-label study of 324 patients, Ueno and colleagues presented data on 48 weeks of therapy with lubiprostone at a dose of 24 mcg twice daily. Of those treated, 30% developed nausea, and 19% developed diarrhea. Compared with baseline, there were improvements in constipation severity, as well as bloating and abdominal discomfort in this population, although no placebo group was included. The results do suggest that treatment efficacy is likely to be maintained for a 1-year period with lubiprostone. Johanson and colleagues investigated whether a subgroup with chronic constipation who fulfilled criteria for IBS had a response to lubiprostone therapy. They reported
data from a pooled subgroup analysis of the phase III lubiprostone placebo controlled 4-week clinical trials. The population comprised only 45 placebo patients and 46 lubiprostone-treated patients who appeared to have IBS with constipation. They found that abdominal bloating and discomfort significantly improved on active therapy compared with placebo in the last 2 weeks of treatment, whereas constipation severity was improved on weeks 1, 3 and 4 significantly. Overall, the efficacy results seemed to be similar in those with IBS with constipation compared with those who did not fulfill IBS criteria. However, this is a subgroup analysis, and the data need to be interpreted very cautiously.

Further experience with tegaserod in chronic constipation was also presented at the meeting. Miner and coworkers explored the role of this drug in patients with severe baseline abdominal pain or bloating. A randomized, double-blind, placebo-controlled trial was performed to assess tegaserod treatment in 2 4-week treatment periods, separated by a treatment-free interval before symptoms recurred. Only patients with at least a partial response to treatment could be entered into the treatment-free interval. Patients with severe abdominal pain or discomfort, or severe bloating at baseline, were significantly improved on tegaserod compared with placebo during initial treatment and when responders were rechallenged. These results suggest that a clinical strategy of retreatment with tegaserod is a reasonable option in responders.

New Treatment for Functional Dyspepsia
Arguably one of the most important new sets of data to be presented at the meeting relates to the results of 2 large clinical trials in functional dyspepsia. Patients in these trials were randomized to either tegaserod 6 mg twice daily or placebo. These patients were all women who had meal-related symptoms, and therefore comprise a subset of functional dyspepsia. Notably, treatment options for patients with meal-related symptoms are currently remarkably limited. The patients were treated with 6 weeks of therapy after a 2-week baseline period. A total of 1360 patients on active therapy and 1307 on placebo were studied. The primary endpoint was percent of days with satisfactory relief of dyspepsia symptoms. The co-primary endpoint was improvement of a composite daily symptoms severity score. A secondary endpoint was global change in dyspepsia symptoms.

The baseline data were similar; the mean age of patients was 44 years. The mean symptom severity score at baseline indicated that patients generally had moderate early satiety, postprandial fullness, or bloating. In terms of the primary endpoint, in the first clinical trial, 32% of patients taking tegaserod versus 27% taking placebo had satisfactory relief of dyspepsia symptoms (median 25% for tegaserod and 10% for placebo). This difference was statistically significant. In the second study there was a similar trend, but it did not reach significance. The composite average daily symptom score significantly decreased in the first study, but in the second study there was just a trend. When the response rates for global assessment of change were examined, in the first study these were significant across 5 of the 6 weeks of therapy. In study 2, these were significant across all weeks of therapy in favor of tegaserod. Pooled analysis suggested that those with moderately severe meal-related symptoms were more likely to respond to tegaserod therapy.

Gastroesophageal Disease
This year’s American College of Gastroenterology Annual Scientific Meeting offered new information on the diagnosis and management of gastroesophageal reflux disease (GERD) and about an evolving disease, eosinophilic esophagitis (EE).

Eosinophilic esophagitis is an increasingly recognized disease classically characterized by intermittent recurrent solid food dysphagia and is seen predominantly in young men. This disease is recognized with increasing frequency and with more diverse presentation. However, most reports have been limited to relatively small series of patients from single institutions. This study used a large pathology database (Pathology Partners, Incorporated, Irving, Texas) to characterize the demographic, clinical, and pathologic features of EE over a more national population. Patients with a mean of 20 or greater
eosphagitis. Patients on long-term proton pump inhibitor (PPI) therapy were less likely to have EE.

Key points:
- In this study, a normal endoscopy does not rule out EE.
- The presence of rings and/or furrows does not guarantee the histologic diagnosis.

This evolving disease will require careful study with attention to endoscopic findings and their histologic correlates. The absence of classic histologic features despite endoscopic suspicion suggests the need for extensive biopsies in these patients. The meaning of eosinophilic infiltration in the absence of endoscopic findings requires further study to determine clinical importance.

A large, multi-center study examined the prevalence of esophageal mucosal pathology and patient satisfaction as a predictor of esophageal mucosal pathology in subjects who used over-the-counter omeprazole magnesium (Prilosec OTC®; Procter & Gamble, Cincinnati, OH). Adults who self-initiated over-the-counter Prilosec for heartburn for ≥ 2 days per week and ingested ≥ 14 over-the-counter Prilosec tablets in the previous 4 months were eligible for study. Subjects were excluded if they used OTC Prilosec for ≥ 15 consecutive days, had received care for heartburn, or had a history of a previous endoscopy or known esophageal pathology. Patients completed a questionnaire designed to assess symptoms, satisfaction with treatment, and other related outcomes. One thousand twenty-four patients, predominantly whites and Hispanics, were included in the intention-to-treat group.
Esophageal mucosal pathology was seen in 33%, most predominantly erosive esophagitis (30.4%). A minority had Los Angeles grades C or D (4%). Close to 2% had Barrett’s esophagus, 3% esophageal stricture, and 1 patient had esophageal cancer discovered on the endoscopy. Treatment satisfaction with the over-the-counter PPIs did not distinguish between subjects with and without esophageal mucosal pathology. The study reminds us that a substantial number of consumers who use over-the-counter PPIs may have important mucosal abnormalities. Symptom relief is not predictive of the presence or absence of these abnormalities, even in this group.

Esophageal acid exposure time during sleep in patients with non-erosive reflux disease, erosive esophagitis, and Barrett’s esophagus were studied. Twenty-four hour esophageal pH testing was performed in 50 patients (non-erosive, n = 20; erosive esophagitis, n = 17; Barrett’s esophagus, n = 13). All groups demonstrated increased esophageal acid exposure time, predominantly in the first half of the sleeping period (first 4 hours). Reflux began an average of 92 minutes after the last meal before sleep. Barrett’s patients had higher acid exposure throughout the sleep period compared to the other groups. The importance of reflux in the early part of the sleeping period is enforced and has important implications for therapy. The majority of patients had their last meal over 90 minutes before sleep, yet had substantial reflux in the overnight period.

Twenty-four hour esophageal pH monitoring was used to determine if continuous positive airway pressure (C-PAP) decreases nocturnal reflux in patients with obstructive sleep apnea.17 Seven of 11 reached a “normal” level of nocturnal esophageal acid exposure. There was a statistically significant improvement in percent time esophageal pH < 4 in the entire group. Sleep indices improved in all 16 patients. A second study addressed this same issue using 48-hour telemetry capsule pH monitoring during a sleep study in 29 patients undergoing a workup for sleep apnea.54 Patients spent the first night without C-PAP and the second with C-PAP. Twenty-seven patients reported heartburn, and 17 reported esophagitis. C-PAP significantly reduced the number of reflux episodes and total time pH < 4 compared to baseline with no C-PAP. These novel studies highlight the potential for this intervention in this difficult-to-manage group and the importance of pH monitoring in documenting the improvement. Long-term studies are needed.

Are pH studies in patients symptomatic on PPIs best performed on or off antisecretory therapy? This study extended previous observations by using a 4-day catheter-free pH recording in which the researchers combined on and off therapy pH monitoring.55 Four-day telemetry capsule pH (N = 15) monitoring (2 days off and 2 days on PPI therapy) was performed. Omeprazole sodium bicarbonate 40 mg was given orally twice daily on days 3 and 4. Four days were recorded in all patients. All patients normalized esophageal acid exposure by day 4. The study demonstrates the potential for prolonged monitoring and its feasibility. Modification of the catheter-free technology for more extended recording might allow this to be practical in the clinical arena.

The pathogenesis of GERD symptoms in patients on high-dose acid-suppressive therapy is not known. Symptoms that may be due to non-acid reflux (or continued acid reflux) are associated with normal numbers of reflux episodes. Multichannel intraluminal impedance/pH studies in patients on twice-daily PPI were viewed to determine the characteristics of reflux episodes that might produce symptoms.56 Seventy-six impedance/pH studies were reviewed (2998 episodes), and 402 patients were determined to be symptomatic (preceded by a reflux episode within 2 minutes of the symptom). Using a multivariate model controlling for age, gender, acidity, and change in pH, reflux height was the only variable positively associated with symptom production. Reflux at 10 cm above the lower esophageal sphincter had the highest likelihood for symptoms compared to the lowest level. This suggests that reflux to the proximal esophagus may be the genesis of PPI refractory symptoms, whether due to distention or greater “sensitivity” of this part of the esophagus to acid or any volume.

[Philip O. Katz, MD, FACP, FACG]

Ulcerative Colitis

Although there was a paucity of presentations regarding the etiology of ulcerative colitis (UC), Albery and Crowe57 described interesting preliminary data regarding the role of T regulatory cells in the pathogenesis of this disease. In a case control study of pediatric patients undergoing endoscopy for suspected inflammatory bowel disease (IBD), tissue sections from subjects with UC and controls were stained with anti-FoxP3 antibody and read by a blinded pathologist. In contrast to control subjects, patients with UC consistently lacked a
The investigators suggested that immune dysfunction in IBD may be related to a paucity of regulatory T cells and propose FoxP3 staining as a "clinical adjunct" for early cases of IBD.

including C-reactive protein (CRP) as well as erythrocyte sedimentation rate and platelet counts as inflammatory markers in consecutive UC patients hospitalized for severe UC. Among the 42 patients, 13% had no elevation in any of the 3 markers. CRP was most consistently elevated (in 78%), but the investigators emphasized the need for improved markers to correlate with clinical and surgical outcomes. The second study evaluated independent scoring of endoscopic severity on results of a therapeutic trial to potentially counter the impact of interobserver variation in endoscopic severity on trial output. Video endoscopy was used to evaluate 335 patients in a clinical trial according to the "Mayo" scoring system. In the series, the blinded observer disagreed with the investigator scoring for endoscopic disease severity 12% to 23% of the time. The study demonstrated the possibility of using an independent observer based on video endoscopy to control for interobserver variations and biases.

The patient’s perspective of living with UC was evaluated by Ed Loftus from the Mayo clinic, who used a large Internet-based cross-sectional survey of a random sample of members of the Crohn’s and Colitis Foundation of America. Of the 49,410 members surveyed, replies were received from 1595 (3%), 74% of whom reported at least 1 UC flare during the previous year. Nearly half the respondents reported key changes in their lifestyles due to major concerns of loss of bowel control (60%) and decreased energy (49%). Two thirds of the respondents disclosed poor compliance with medications related to dosing frequency, number of pills, and inconvenience with medications (likely rectal administration). From the standpoint of an “ideal” therapy, 97% replied that high efficacy was “very important” whereas 74% said that lack of side effects was very important. Non-rectal dosing (36%), low cost (23%), fewer pills (23%), and less frequent dosing (23%) were additional ideal attributes described as very important.

Quality of life was also assessed in several poster presentations. Sandborn and colleagues reported on the further improvement in quality of life attained by steroid sparing in addition to achieving clinical remissions from patients enrolled in the Active Ulcerative Colitis 1 and 2 (ACT 1 and ACT 2) trials of infliximab for UC. Among 408 patients on steroids at baseline, 91 were in remission at week 30 and 70 of 91 had discontinued steroids. Among patients in remission at week 30, the investigators reported that those who discontinued steroids had more improvement in their Inflammatory Bowel Disease Questionnaire scores and physical component of the SF-36 than those in remission while still receiving steroids. Further analysis from the same trials also demonstrated that the long-term (1-year) effect of infliximab was improved in patients receiving infliximab in the ACT 1 and ACT 2 trials and was independent of the baseline disease severity.

Two poster presentations highlighted potential complications related to UC or surgery for treatment or complications of the disorder. Jackson and associates reported on 9 IBD patients who developed a mesenteric vascular thromboembolism, 4 of whom had UC. More than half were in remission at the time of diagnosis, and 4 patients had the catastrophic complication of short bowel syndrome. In contrast, Loftus and colleagues reported on complications of colectomy in 215 patients from a database report. The investigators reported a wide variety of complications, including fistulas (9%), abscesses (21%), sepsis/pneumonia/bacteremia (12%), and a revision of an ileostomy or colostomy (2.3%), all within the first 6 months after surgery.

Shifting gears from quality of life to costs of care, several poster presentations described cost and utilization issues in UC. As would be expected, health care costs for a cohort of...
patients from a database of a self-insured employer demonstrated that direct costs for UC patients were related to disease severity and overall were approximately twice those of enrollees without UC. Indirect costs for disability claims were incurred by 20% of the employees with UC. Additional posters documented that the increased costs were identified in pediatric patients and adults, including patients over the age of 65. As has been previously demonstrated for IBD costs, in general, hospitalizations account for the highest overall costs and therapies that reduce hospitalizations (and surgeries) are likely to reduce overall costs for UC therapy.

Dr. Lichtiger reported that 80% of hospitalized patients had clinical remissions induced by cyclosporine and that after the introduction of 6-mercaptopurine, 53% of these patients remained well, with a mean follow-up of nearly 9 years.

Whether infliximab (or other anti-tumor necrosis factor therapies) ultimately will reduce hospitalization costs for UC remains in question despite the ACT 1 and 2 clinical trials. As investigators from the Mt. Sinai Hospital in New York reported, of 42 patients with UC treated with infliximab, 71% had a clinical response as measured by decreases in stool frequency and/or bleeding, only 22% were in remission, and less than 25% had remitted and were off steroids. In the short-term study, 22% of patients required a colectomy. Hence, although these findings are consistent with the controlled trial data from ACT 1 and 2, the overall improvement and the 33% of patients off corticosteroids may not translate into long-term avoidance of surgery.

In contrast to infliximab, which has been highly effective for patients with moderate to severe UC in the outpatient setting, cyclosporine has been very effective for patients hospitalized for severe UC. Simon Lichtiger, one of the pioneers of cyclosporine therapy, provided an update on his personal experience treating 144 UC patients with cyclosporine therapy. In his oral presentation, he reported that 80% of hospitalized patients had clinical remissions induced by cyclosporine and that after the introduction of 6-mercaptopurine (6-MP), 53% of these patients remained well, with a mean follow-up of nearly 9 years. In his series, severe adverse effects occurred in 4 patients and included a grand mal seizure; acute renal failure, sepsis, and death; disseminated cytomegalovirus; and a

Crohn’s Disease

Crotolithum pegol is a humanized anti–tumor necrosis factor (anti-TNF) Fab’ fragment linked to polyethylene glycol (PEG).

Higher remission and maintenance of response rates with subcutaneous monthly crotolithum pegol in patients with recent-onset Crohn’s disease: data from PRECiSE 2: The PRECiSE 2 trial was a placebo-controlled trial of crotolithum pegol maintenance therapy in 668 patients with Crohn’s disease. Adult patients with moderately to severely active Crohn’s disease received a loading dose regimen consisting of 3 open label induction doses of crotolithum pegol 400 mg at weeks 0, 2, and 4. Four hundred twenty-eight patients who were in clinical response at week 6 were randomized to receive maintenance therapy with crotolithum pegol 400 mg or placebo every 4 weeks through week 24. The clinical response rates at week 26 (primary endpoint) were 36% for placebo and 63% for crotolithum pegol (P < .001); the clinical remission rates at week 26 were 29% and 48% (P < .01). An exploratory analysis was performed to determine if the early use of crotolithum pegol would result in improved treatment outcomes. The rates of response at week 26 to crotolithum pegol and placebo were 90% and 37% for patients with
Crohn’s disease duration of less than 1 year; 75% and 50% for disease duration of 1 to less than or equal to 2 years; 62% and 36% for disease duration 2 to less than or equal to 5 years; and 57% and 33% for disease duration of more than 5 years. Likewise, the rates of remission at week 26 to certolizumab pegol and placebo were 68% and 37% for patients with Crohn’s disease duration of less than 1 year; 55% and 36% for disease duration of 1 to less than or equal to 2 years; 47% and 29% for disease duration 2 to less than or equal to 5 years; and 44% and 24% for disease duration greater than 5 years. Certolizumab pegol was effective in patients who had previously received infliximab and then lost response or became intolerant.

Certolizumab pegol was effective in patients who were naïve to anti-TNF therapy with infliximab and patients who had previously received infliximab.\(^7^9\) Certolizumab was also effective in patients receiving concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate, and those not receiving immunosuppressive therapy.\(^7^9\) Significant improvements in health status (as measured by SF-36 and EuroQol-5) and quality of life were also observed in patients treated with certolizumab pegol.\(^8^0,8^1\) Certolizumab pegol 400 mg every 4 weeks is effective for maintenance of response, remission, health status, and quality of life in patients with moderately to severely active Crohn’s disease irrespective of concomitant immunosuppressive therapy and prior infliximab therapy. Early therapy with certolizumab pegol (within 0 to 2 years of diagnosis) has the potential to markedly improve maintenance of response and remission rates.

Adalimumab is a fully human monoclonal antibody against TNF-\(\alpha\). Adalimumab rapidly induces clinical remission and response in patients with moderate to severe Crohn’s disease who had secondary failure to infliximab therapy: results of the GAIN study: The GAIN study was a placebo-controlled trial of adalimumab induction therapy in adult patients with moderately to severely active Crohn’s disease who had previously responded to infliximab and then lost response or became intolerant.\(^8^3\) Three hundred twenty-five patients who had previously responded to infliximab and then lost response or became intolerant were randomized to treatment with a subcutaneous loading dose induction regimen of adalimumab 160 mg at week 0 and 80 mg at week 2 or placebo. This loading dose induction regimen, which was designed to achieve steady-state blood concentrations of adalimumab by 2 weeks similar to those achieved with 40 mg every-other-week maintenance dosing, has previously been demonstrated to induce clinical response.\(^8^3\)

Eight hundred fifty-four patients (499 of 854) who received open-label adalimumab responded at week 4 and were randomized to maintenance treatment through week 56 with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg every week.\(^8^4,8^5\) The co-primary endpoints for the study were induction of clinical remission at weeks 26 and 56. The rates of remission at week 26 were 17% in the placebo group and 40% and 46% in the adalimumab 40 mg every other week and 40 mg weekly groups (\(P < .001\) for both comparisons vs placebo). The rates of remission at week 56 were 12% in the placebo group and 36% and 41% in the adalimumab 40 mg every-other-week and 40 mg weekly groups (\(P < .001\) for both comparisons vs placebo). Maintenance therapy with adalimumab increased the rate of remission free of corticosteroids at week 26 (3% in the placebo group vs 35% and 30% in the adalimumab 40 mg every-other-week and weekly groups) and at week 56 (6% in the placebo group vs 57% and 54% in the adalimumab 40 mg every-other-week and weekly groups).
29% and 23% in the adalimumab 40 mg every-other-week and weekly groups).66 Adalimumab was effective in patients who were naïve to anti-TNF therapy with infliximab and patients who had previously received infliximab.67 Adalimumab was also effective in patients receiving concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate, and those not receiving immunosuppressive therapy.67 Closure of all fistulas at the final 2 visits occurred in 14% of placebo-treated patients, 36% of patients receiving adalimumab 40 mg every other week, and 46% of patients receiving adalimumab 40 mg weekly.68 Adalimumab 40 mg every other week and 40 mg weekly is effective for maintaining response and remission, remission free of corticosteroids, and closing fistulas and maintaining fistula closure in patients with moderately to severely active Crohn’s disease who respond to induction therapy with adalimumab 80 mg at week 0 and 40 mg at week 2. Response to adalimumab is not dependent on whether the patient has been treated with infliximab or is currently receiving immunosuppressive therapy.

Natalizumab is a humanized monoclonal antibody to the α4 integrin.

Natalizumab maintains remission for 2 years in patients with moderately to severely active Crohn’s disease and in those with previous infliximab exposure: results from an open-label extension study: Three Phase 3 studies have been conducted to evaluate natalizumab for induction (ENACT 1 and ENCORE) and maintenance (ENACT 2) of response and remission in patients with moderately to severely active Crohn’s disease.89,90 In the ENACT 2 trial, patients with moderately to severely active Crohn’s disease who received induction therapy with natalizumab 300 mg at weeks 0, 4, and 8 and responded at weeks 10 and 12 were re-randomized to maintenance therapy with natalizumab 300 mg or placebo every 4 weeks through week 60.89 Sixty-one percent of patients in the natalizumab group maintained response through week 36, compared to 28 percent in the placebo group (P < .001).89 Remission was maintained through week 36 in 44% of patients in the natalizumab group versus 26% in the placebo group (P = .003). The results through week 60 were similar. Eighty-seven patients who were in remission at week 60 after 60 continuous weeks of natalizumab therapy entered an open-label extension study and continued natalizumab 300 mg every 4 weeks for an additional 12 months. Seventy-five of these 87 patients (86%) were still in remission after 12 additional months of therapy.91 When natalizumab was subsequently reintroduced during the open-label extension trial, antibodies to natalizumab developed in only a minority of patients who experienced interruption of natalizumab dosing during the ENACT 2 trial.92 The use of natalizumab in patients with multiple sclerosis and Crohn’s disease has been complicated by the report of 3 cases of multifocal leukoencephalopathy caused by the human polioma JC virus in patients treated with natalizumab, with an estimated risk of 1:1000.93-96 The FDA approved natalizumab for multiple sclerosis with the requirement of mandatory participation in a risk management and registry program called the TOUCH program. It is expected that natalizumab will be submitted to the FDA for review regarding a treatment indication for refractory Crohn’s disease in 2007.

Intestinal transplantation for end-stage Crohn’s disease: therapeutic efficacy and risk of recurrence: Between May 2, 1990 and March 31, 2006, a total of 196 consecutive adult patients underwent intestinal transplantation at the University of Pittsburgh.97 Thirty-eight of 196 patients had Crohn’s disease. Simultaneous liver transplantation was required in 9 patients (26%). The cumulative overall survival of patients with Crohn’s disease was 85% at 1 year and 62% at 3 years. Changes in the induction immunosuppression regimen have led to significant improvement in survival, with 1- and 3-year survival rates of 92% and 78%, respectively. Histologic evidence of recurrent Crohn’s disease in the allograft was seen in 3 patients (7.5%) after 3, 15, and 18 months. Survival after intestinal transplantation for end-stage Crohn’s disease has improved and transplantation now represents a viable treatment option for selected patients.

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