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American College of Gastroenterology 65th Annual Scientific Meeting

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Goal

The goal of these activities is to define "state-of-the-art" treatment protocols and clinical strategies for the prevention, diagnosis, and management of diseases of the gastrointestinal tract and liver, to enhance the care of individuals with these diseases and support quality clinical practice of healthcare professionals involved in their care.

Learning Objectives

These summaries are intended for physicians, nurses, and other healthcare professionals conducting research and/or providing primary or specialty care for individuals with diseases of the gastrointestinal tract and liver.

Upon completion of this self-study activity, participants will be able to:

1. Summarize the latest trends and topical issues in the fields of gastroenterology and hepatology.
2. Evaluate new diagnostic or therapeutic strategies as they relate to specific clinical entities, including inflammatory bowel disease, irritable bowel syndrome, hepatitis C, and Barrett's esophagus/esophageal adenocarcinoma.
3. Define established and new forms of therapy for diseases of the gastrointestinal tract and liver.
4. Discuss the latest advances in diagnostic and therapeutic endoscopy.
5. Define current concepts in the pathophysiology of diseases of the gastrointestinal tract and liver as they influence the approach to clinical management and affect clinical outcome.
6. Integrate information regarding the diagnosis, prognosis, treatment, and pathophysiology of diseases of the gastrointestinal tract and liver to enhance patient care and improve clinical outcomes.

Eligibility for Credit

Continuing education credit will be awarded to physicians, physician assistants, registered nurses and nurse practitioners who successfully complete this activity as described in the section Instructions for Credit. Certificate is defined as a record of participation. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing boards.

Instructions for Credit

Participation in this self-study activity should be completed approximately two (2.0) hours. To successfully complete this activity and receive credit, participants must follow these steps during the period from November 2, 2000 through November 2, 2001

1. Register for continuing education credit by completing the "registration" process.
2. Read the learning objectives.
3. Read the article text and tables, and figures.
4. Read, complete, and submit answers to the post test questions and evaluation questions. Participants must receive a test score of at least 70%, and respond to all evaluation questions to receive a certificate.
    - If an instant certificate is available for the activity, you will be presented with your certificate on your screen. You may print the certificate, but you cannot alter the certificate. Your credits will be tallied in the CME Tracker, and you

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Inflammatory Bowel Disease Treatment: Effectiveness, Safety, and Adherence

Bret A. Lashner, MD

Introduction

Much has been learned in recent years about the use of old and new therapies for treating inflammatory bowel disease (IBD). New therapies (eg, infliximab) and better monitoring of older drugs (eg, 6-mercaptopurine or azathioprine) have advanced our treatment options for this disease entity. The

annual meeting of the American College of Gastroenterology held in New York City from October 16-18, 2000, provided a forum for investigators to continue discussions on both their experiences and the latest insights into therapy for IBD. A symposium conducted during this meeting concentrated on safety and adherence issues regarding IBD therapy. The following report summarizes the key clinical findings presented at that symposium and highlights important podium and poster presentations that further contribute to a better understanding of the challenges facing the physician treating the patient with IBD.

Infliximab: Efficacy and Safety Issues

Stephen B. Hanauer, MD, from the University of Chicago, discussed the effectiveness and toxicity experience with more than 60,000 infusions of infliximab (*Remicade*) given to patients with Crohn's disease in the United States since the drug was approved for clinical use by the FDA in 1998. Infliximab is a chimeric, monoclonal antibody directed against tumor necrosis factor-alpha (TNF-alpha) that demonstrates a high specificity and affinity to TNF-alpha. Results of a number of studies have suggested a central role for TNF-alpha in chronic intestinal inflammation.

In general, the effectiveness of infliximab in clinical practice has been comparable to that reported in the clinical trials. Thus, a single infusion of infliximab (5 mg/kg) given to a patient with inflammatory-type Crohn's disease can be expected to improve as many as 80% of patients and induce remission in approximately one third of all patients. For fistulous Crohn's disease, 3 infusions given over 6 weeks can be expected to decrease drainage in 70% and completely close fistulas in approximately 50% of cases. Based on the University of Chicago experience with 203 patients with Crohn's disease, infliximab appears to be steroid-sparing.

Investigators from Lenox Hill Hospital and Mount Sinai Hospital in New York, Brown University School of Medicine, Beth Israel Deaconess Medical Center, and the Cleveland Clinic confirmed these response rates in adults and children.[1-4] Additionally, Chey and colleagues[5] from the Rochester Institute for Digestive Diseases and Sciences showed that infliximab was effective in 16 of 17 patients treated for ulcerative colitis. Unfortunately, these remarkable findings seem to wane 12 weeks following the last infusion. Whether repeated "maintenance" infliximab infusions or institution of high-dose immunosuppressive therapy at the time of infusion will successfully maintain remission has yet to be established.

Careful selection of patients for infliximab infusion should increase response rates and minimize cost and toxicity by avoiding administration of the drug to patients less likely to respond. Brzezinski and colleagues[4] from the Cleveland Clinic found that individuals who smoked cigarettes and those not on immunosuppressive medications were less likely to respond to therapy with infliximab, especially patients with inflammatory-type disease. By contrast, Rawlins and colleagues[6] from the Virginia Mason Clinic failed to confirm a better treatment effect in patients taking azathioprine, 6-mercaptopurine, or methotrexate. Rusche and colleagues[7] from the Indiana University Medical Center demonstrated a better response rate to infliximab in patients with ileocolic or colonic Crohn's disease vs those with small bowel disease.

The use of infliximab in the appropriate patient populations -- despite issues of cost -- can lead to good savings overall for the healthcare system potentially by decreasing need for gastrointestinal surgery by 15%, the need for endoscopies by 34%, and emergency department visits by 63%.[8]

Adverse Events

Although clinical trials of infliximab report that up to 15% of patients developed human anti-chimeric antibody (HACA), no differences in adverse effects among treated and placebo groups were found. The rate of HACA-positivity may be diminished by concomitant administration of immunosuppressive therapy. Adverse events were primarily acute, minor, and could be treated during infusion with diphenhydramine or, alternatively, by slowing the rate of infusion. Fortunately, severe antibody-mediated reactions such as asthma, hives, or anaphylaxis are very rare. It is unknown whether antibody-mediated reactions are related to HACA, but it is reasonable to withhold infliximab infusions in patients who are positive for the now commercially available HACA. Serious delayed hypersensitivity reactions, usually characterized by arthritis at least 7 days after the infusion, can be observed in a minority of patients who are reinfused more than 3 months after an initial infusion.

The importance of anti-TNF therapy in Crohn's disease was further underscored by Kim and colleagues[9] from the Medical College of Wisconsin. These investigators found that thalidomide was effective in patients who could not tolerate infliximab. What is the relevance of thalidomide in this setting? Thalidomide, a teratogen that has recently shown efficacy in the treatment of leprosy, also has anti-inflammatory effects. Another adverse effect associated with infliximab is the apparent development of fibrous strictures in 9% (7/76) of patients within a median of 30 days after the inflammation is successfully treated.[10]

Research is currently underway to expand the indications for infliximab in the IBD setting to include ulcerative colitis, pyoderma gangrenosum, and ankylosing spondylitis.

6-Mercaptopurine and Azathioprine: The Utility of Metabolite Monitoring

Background and Significance

Immunomodulating agents that suppress the immune system and thus downregulate inflammation, such as 6-mercaptopurine (6-MP) and azathioprine (AZA), are important in the long-term treatment of IBD. What is the rationale for the use of immunomodulators in this setting? The rationale stems from observations implicating immunologic mechanisms in the pathogenesis of IBD.

Ernest G. Seidman, MD, from Sainte Justine Hospital in Montreal, presented the latest findings on the clinical utility of measuring 6-MP and AZA metabolites in patients undergoing treatment for IBD. 6-MP and AZA are now 2 of the most widely used drugs for IBD because of their efficacy in both inducing and maintaining remission and their favorable adverse event profile. Data from 3 studies conducted by investigators at Lenox Hill Hospital confirmed the safety of short- and long-term 6-MP (with the exception of an increased risk of malignancy in patients with sustained leukopenia [WBC < 4000/mm^3 for at least 3 weeks]).[11-13] Approximately 8% of patients on 6-MP or AZA will develop acute pancreatitis and 1% will develop allergy characterized by fever, rash, and abdominal pain. About 10% will develop leukopenia and thus need to have doses adjusted downward. 6-MP and AZA can take up to 3 months or longer to reach efficacy, creating a clinical dilemma in nonresponding patients.

Are patients who fail to respond being inadequately dosed or have they simply not taken the drug long enough to have an opportunity to respond? In previous years, clinicians have escalated the dose until

mild leukopenia (WBC < 5,000/mm^3) was induced. As compared to patients without leukopenia, leukopenic patients were more likely to respond, more likely to have their dose of steroids reduced, and more likely to be adequately treated for complications of IBD. However, this "crude" measure of drug level is not an acceptable practice because not everyone who is dosed adequately will become leukopenic, and toxic doses could be given before leukopenia develops.

Strategies for Monitoring Therapy

Technology is now available that allows for more accurate dosing of 6-MP and AZA. The technology also offers clinicians the opportunity to find the very narrow window between efficacy and toxicity for these medications. The end products of the metabolic pathways for these immunosuppressants and an important metabolizing enzyme have become very useful in managing patients with IBD (see Figure).

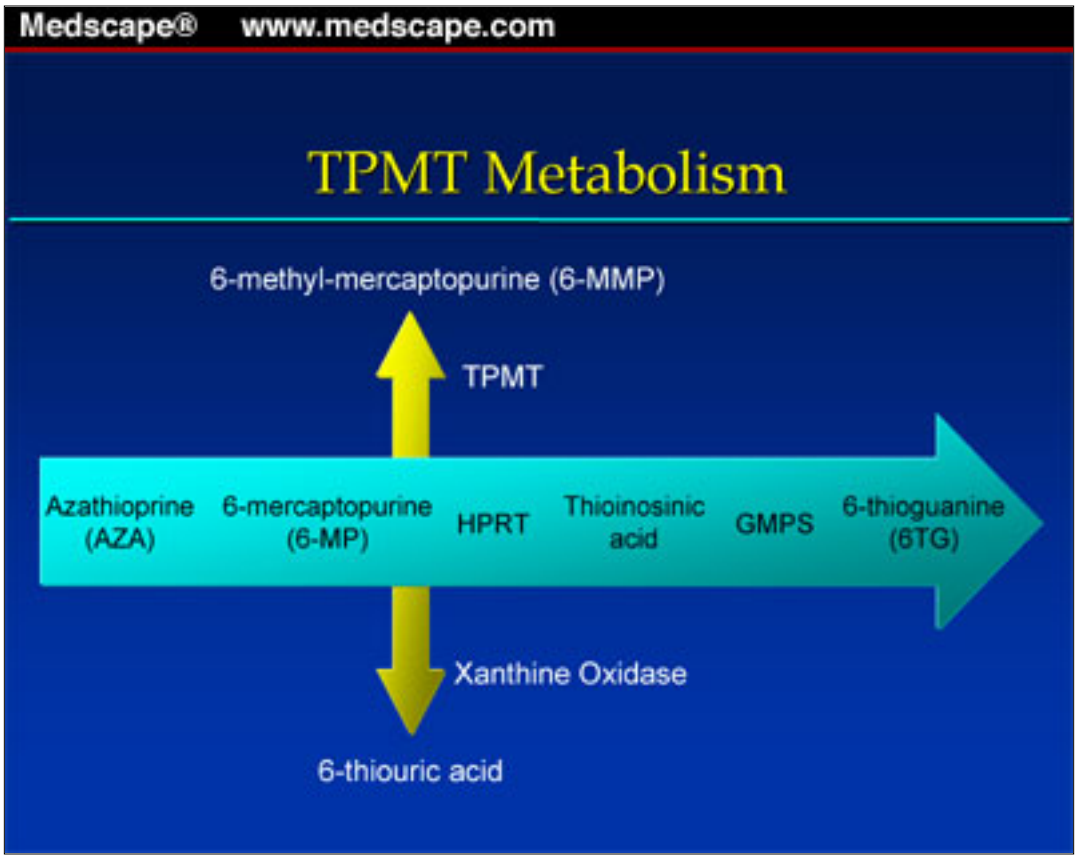

Figure. The metabolic pathway of azathioprine and 6-mercaptopurine.

AZA is converted to 6-MP during the first pass of this drug through the liver. 6-MP is further metabolized to 6-thioguanine (6-TG), the active metabolite that can be measured in blood. 6-TG levels greater than 235 pmols/8x10^8 cells have been shown to correlate with response to 6-MP. Achkar and colleagues[14] from the Cleveland Clinic Foundation proposed that 6-TG levels greater than 260 pmols/8x10^8 cells should be the preferred cutoff for therapeutic effectiveness. Moreover, these investigators demonstrated that 6-TG levels were more strongly associated with response than either immunosuppressant dose or WBC less than 5000/mm^3.

6-MP is inactivated by 2 pathways: metabolism by xanthine oxidase and by thiopurine methyltransferase (TPMT). Xanthine oxidase metabolizes 6-MP to the inactive thiouric acid. Patients on allopurinol, a xanthine oxidase inhibitor, should be given immunosuppressants with caution, probably at very low doses. Measuring 6-TG levels would be extremely helpful in such patients. Milk contains xanthine

oxidase and patients whose 6-TG levels are low despite relatively high doses of the medication should be advised to minimize milk consumption. 6-MP is also metabolized to the inactive 6-methylmercaptopurine (6-MMP) by TPMT. 6-MMP levels greater than 5700 pmol/8x10^8 cells have been associated with hepatotoxicity, but transient hypertransaminasemia is seen only in a minority of patients. Immunosuppressive medications need not be discontinued if patients are found to have very high levels of 6-MMP and normal liver function tests, but careful monitoring of liver function is essential.

Dubinski and colleagues[15] from Cedars-Sinai Medical Center presented their work on 6-TG in the treatment of patients with active Crohn's disease who are found to have very high levels of 6-MMP. These patients have an abnormal metabolism of 6-MP such that too much of the inactive 6-MMP is produced and insufficient 6-TG is produced in order to have a therapeutic effect. Providing 6-TG directly to 9 patients with IBD (6 with Crohn's disease and 3 with ulcerative colitis), Dubinski showed a response in 7 and remission in 6. One patient developed leukopenia and none developed or had recurrence of hepatotoxicity. Alternatively, TPMT activity can be diminished when 5-aminosalicylic acid (5-ASA) products are administered. Markowitz and colleagues[16] from the North Shore-Long Island Jewish Health System showed that 2 patients with high 6-MMP and low 6-TG could have their metabolite profile improved by coadministering 5-ASA.

Metabolite levels need not be checked in every patient. There are 2 populations, however, for which monitoring metabolite levels could prove extremely important in improving patient care and outcome: 1) Metabolite levels should be checked in patients who fail to respond to immunosuppressive therapy to distinguish the true nonresponders from those who are inadequately dosed and from patients who are not adherent to their medication regimens. Therapy can be changed or abandoned based on the results. 2) Monitoring metabolite levels would be helpful for patients whose remission is being maintained by 6-MP or AZA. The chances of remission being maintained are likely to be greatest when 6-TG levels are within the therapeutic range.

Studies for determining levels of TPMT are also available commercially. TPMT is absent in 1 in 300 individuals and, because of the risk of severe toxicity, immunosuppressive therapy should be avoided in them. Eleven percent of the population has lower-than-normal levels and should therefore have immunosuppressants administered at doses lower than what would be given normally. TPMT levels should be checked in all patients being considered for administration of high-dose oral (6-MP 1.5 mg/kg/day or AZA 2.5 mg/kg/day) or intravenous immunosuppressive therapy. Mahadevan and colleagues[17] from the Mayo Clinic showed that intravenous AZA given to 9 patients with severely active ulcerative colitis enabled 5 of these patients to avoid colectomy and 3 to achieve remission. All such patients should have TPMT levels measured prior to administration of intravenous AZA.

Pregnancy and Nursing: Safety of Commonly Used IBD Drugs

Bret A. Lashner, MD, from the Cleveland Clinic, discussed the available information on the safety of IBD medications in pregnant women. There is a scarcity of controlled trials in pregnant patients with IBD because of the potential liability associated with this population. Moskovitz and colleagues[18] from the Mount Sinai School of Medicine in New York reported on 231 pregnancies among 120 patients with IBD. In these pregnancies, there was a 6% occurrence of prematurity, a 21% occurrence of spontaneous abortion, and a 2.6% occurrence of major birth defects; medications were not associated with a poor outcome.

What Do We Know?

There are no IBD drugs listed as Category A (controlled studies in women fail to show a fetal risk). Still, it is generally believed that corticosteroids and all 5-ASA products are safe and should be used if necessary in pregnant women. Steroids are considered Category C drugs (fetal risk unknown; ie, either definite fetal risk in laboratory animals has been shown and no studies in women are available, or no studies in animals or women have been done) and 5-ASA products are considered Category B drugs (some fetal risk in laboratory animals has been demonstrated but either no risk has been found in controlled trials in women or no studies are available). Potentially, sulfasalazine, being a sulfa drug that crosses the placenta and is passed in breast milk, could displace bilirubin from albumin, thereby putting the baby at an increased risk for kernicterus. Fortunately, kernicterus has never been observed in babies of mothers on sulfasalazine and, for this reason, it therefore need not be avoided. Sulfasalazine does, however, competitively inhibit folic acid absorption, and pregnant women on sulfasalazine thus need to be supplemented with folic acid to minimize the risk of neural tube defects. Topical 5-ASA has been shown to be safe during pregnancy.

Considerable controversy exists concerning the use of 6-MP or AZA. Both are listed as Category D drugs, meaning that there is a definite risk to the fetus. Therefore, these agents should only be used if the risk of not treating the mother with these medications outweighs the risk to the fetus. These drugs interfere with purine biosynthesis and are especially toxic to rapidly dividing cells. In laboratory animals, 6-MP and AZA are associated with cleft palate, limb malformations, and ocular abnormalities. In women on these immunosuppressants for organ transplantation or systemic lupus erythematosus, there appears to be no increased risk of congenital abnormalities -- but there is a risk for growth retardation and prematurity. In IBD patients, there are few case series that document prematurity and spontaneous abortions in women who were taking 6-MP and AZA and congenital abnormalities when fathers were taking 6-MP. However, the number of patients in these studies is small and the number of complications observed is exceedingly small as well. Dr. Lashner recommended that, if at all possible, women be switched from 6-MP or AZA to steroids and 5-ASA agents during their pregnancy and then be switched back after delivery.

There is so little information on infliximab in pregnancy that it is listed as a Category C drug. Cyclosporine also is listed as a Category C drug, despite the fact that there is some risk in laboratory animals; there are no studies in women. Metronidazole (Category C) is teratogenic in animals, especially in the first trimester, and should therefore be avoided early in pregnancy. Methotrexate is listed as Category X due to teratogenicity and the general consensus that the risks to the fetus outweigh any benefits to the mother; this drug must be avoided during pregnancy and breastfeeding.

Conclusions: What Should and Shouldn't Be Used to Treat the Pregnant Patient With IBD?

In summary, all 5-ASA products and corticosteroids appear to be safe during pregnancy and nursing. Methotrexate is contraindicated, and all other drugs should be used only if the benefits to the mother outweigh any possible risk to the fetus.

Adherence to Recommended IBD Therapy

Sunanda V. Kane, MD, from the University of Chicago, continued the trend with a discussion on strategies for improving patient adherence to recommended therapy. "Adherence" is a preferable term to "compliance" because the former implies a reciprocal interaction between patient and physician. Adherence can be defined as the extent to which patient behavior coincides with medical advice. In most chronic diseases, including IBD, nonadherence ranges between 25% and 50%. Fully 40% of ulcerative colitis patients do not take sulfasalazine as prescribed. There are many reasons for nonadherence, including too-frequent dosing regimens, excessive medication expense, adverse drug effects, and failure to realize the importance of maintenance therapy (including cancer surveillance colonoscopy) for patients who feel well.

The key to improving adherence to therapy centers on patient education by medical professionals. Fully one third of IBD patients feel the need to seek alternative medical therapy (eg, acupuncture, herbal and nutritional supplements, massage, yoga, meditation). [19] Hilsden and colleagues from the University of Calgary reported that alternative medicine advice is often freely dispensed to IBD patients by health food store employees, herbalists, and chiropractors. [20] The more the patient is aware of the nuances of IBD and its sequelae, as learned from discussions with his or her physician, the more likely that patient will adhere to therapeutic recommendations.

Also, simplifying oral regimens to twice daily, choosing less expensive medications, insisting on follow-up clinic visits, and encouraging attendance at health talks or support groups are strategies likely to improve adherence. Monitoring prescription refills and drug metabolite levels may be useful, especially in patients who are not responding as expected to therapy.

Conclusions and Implications for Clinical Practice

We have entered a new era in the therapy of IBD. The success of new drugs such as the biologic agent infliximab has driven the pharmaceutical industry to investigate other strategies for interrupting the unchecked inflammatory process that underlies the disease. Drug development in IBD has not yet peaked -- there is much more on the way. Additionally, with immunosuppressive metabolite monitoring we can now better dose patients and follow adherence than we ever could in the recent past. Very directly, new ideas have led to better therapy. And, as our experience has grown, use of potentially toxic agents in pregnancy and nursing has become less uncertain than it once was.

Overall, data presented at the annual meeting of the American College of Gastroenterology show that as our therapeutic options and experience continue to expand, we are significantly improving the care of the patient with IBD.

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New Developments in Endoscopy

Charles J. Lightdale, MD

Introduction

The enormous impact of endoscopy on the practice of gastroenterology was highlighted in 2 major clinical symposia held at this year's Annual Meeting of the American College of Gastroenterology. The first of these programs focused on updates of currently available, yet evolving, endoscopic methods. Concordant with the shift of endoscopy from a strictly diagnostic method to one that includes minimally invasive therapies, 4 of the 5 presentations related to therapeutic endoscopy. The initial focus was on new endoscopic treatments for gastroesophageal reflux disease (GERD), followed by discussions on endoscopic mucosal resection and mucosal ablation using photodynamic therapy and argon plasma coagulation. The session closed with an update on strategies in endoscopic ultrasonography.

Endoscopic Antireflux Procedures

Endoscopic Gastroplasty

The concept of treating GERD using an endoscopic per-oral method burst into prominence this year with the simultaneous approval by the United States Food and Drug Administration (FDA) of 2 new methods for this purpose. These endoscopic therapies were presented in detail by Dr. Steven A. Edmundowicz of Washington University Medical School in St. Louis, Missouri.

The first of the antireflux endoscopic procedures discussed uses an endoscopic "sewing machine" to place sutures in the region of the lower esophageal sphincter (LES) and gastric cardia. The sewing machine involves suction and a needle device to carry a suture through the muscularis propria. The suture is drawn to the outside where a surgical knot is tied. The knot is then pushed down alongside the endoscope using a special knot-pusher device to leave a fixed fold in the wall of the esophago-gastric junction or cardia. The crimped fold narrows and stiffens the area, leading to decreased reflux. Mastery of the technique will clearly require a high level of endoscopic skill, experience, and training with the new instruments.

Dr. Edmundowicz reviewed the 2 main studies carried out thus far that employed endoscopic sewing for treating gastroesophageal reflux. A multicenter trial involving 64 patients showed a reduction in heartburn score from a baseline of 22.8 to 9.2 at 3 months following the procedure ($P < .001$). Similarly, regurgitation score was reduced from a baseline of 1.8 to 0.6 at 3 months ($P < .001$).[1]

In the second trial carried out by the sewing machine's developer, Dr. Paul Swain, London, England, 102 patients with GERD were treated with endoscopic gastroplasty. The baseline symptom score of 5 was reduced to 1 at 3 months ($P< .05$). The length of the LES was increased from 2 cm to 3 cm and the LES pressure increased from 5 mmHg to 8 mmHg ($P < .05$). The time of esophageal pH recordings < 4 was reduced from 8.4% to 2.7% ($P < .05$).[2]

Complications of the sewing procedures were at an acceptable rate. In the first study, there was 1 small perforation and 2 minor overtube injuries. In the second study, there was 1 perforation and dysphagia occurred transiently in 3 patients.

Radiofrequency Energy

In this procedure, multiple foci of radiofrequency energy are delivered to the muscle layer of the esophago-gastric junction and gastric cardia. The technique is carried out with a Stretta device, which employs a balloon from which rows of needles are passed into the area to be treated. Radiofrequency energy is produced at the needle tips using a processor that controls the rate and degree of the resultant injury. The mucosa is simultaneously cooled with infused water to avoid mucosal effect.

An initial multicenter clinical study of the Stretta procedure was performed in 28 patients and resulted in no complications. The need for antacid medication was decreased from a baseline of 100% to 21% at 6 months. The time at esophageal pH < 4 was decreased from 12% to 6.7% (P < .05), heartburn score was decreased from 3.7 to 1.4 (P < .001), and a GERD quality-of-life score was reduced from 24.4 to 7.9 (P < .001).[3]

Injection

There have been several pilot experiments conducted on the endoscopic injection of bland or inert materials into the area of the LES in an attempt to narrow the area and increase sphincter pressure. This method has the appeal of being technically simple, potentially less expensive, and relatively easy to carry out for most gastrointestinal endoscopists. Concerns center around long-term risks and potential migration or reactions over time. Clinical trials have not been reported.

Implications

There is a great deal still to be learned following the early success of endoscopic suturing and radiofrequency treatment for GERD. The best placement of endoscopic sutures has yet to be determined, and outcome differed in the 2 studies presented so far. The mechanism of action of the Stretta procedure has not been fully elucidated. Possibilities include a stiffening effect, which overcomes the distension of the LES that occurs with a meal, or an effect on afferent nerve reflexes at the gastroesophageal junction.

Patient selection may be critical in terms of when and how to carry out these endoscopic antireflux procedures. In any case, there is no doubt that the dramatic introduction of these procedures this year will begin to alter the management of patients with GERD. Pharmacologic therapy, primarily with proton pump inhibitors, and laparoscopic fundoplication have both been highly effective, but each can be unsatisfactory at times. The endoscopic procedures are very new compared with standard medical and surgical therapies, but they do have the potential to be equally effective, less expensive, and less invasive.

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is a technique that was developed and popularized in Japan and has now attracted wide attention among American gastrointestinal endoscopists. In Japan, the method has

been primarily used for early gastric cancer -- which is not a common problem in the United States. However, EMR seems to be a highly safe and effective method with broad applicability for minimally invasive removal of lesions confined to the mucosa throughout the gastrointestinal tract.[4]

Dr. Gregory G. Ginsberg, from the University of Pennsylvania Medical Center, discussed the EMR technique. The key element of this procedure involves lifting the mucosal layer away from the submucosa by injecting fluid, most commonly normal saline solution, into the submucosa. A snare is then placed over the raised area of mucosa, and the mucosa resected with tightening and cautery. Stiff monofilament snare wires or barbed snares make it easier to grasp the raised mucosa. Using a double-channel endoscope, the mucosa can be further lifted using a biopsy forceps inside the open snare for easier grasping and specimen retrieval. This is a variant of the old, risky "lift and cut" method, but with the added safety of the saline cushion.[5]

The most recent variation of EMR uses the lifting power of endoscopic suction by fitting a cap on the tip of the endoscope. Special caps have been manufactured to hold an open snare. After injection, the raised mucosa is suctioned into the cap and the snare closed.[6]

Another variation of this method employs a variceal ligating device to suction the raised mucosa, followed by the application of a ligating band to create a pseudopolyp for snare resection. The banding technique, which has been called "band and snare" or "band and cut," is a bit more cumbersome than standard EMR. However, the equipment is widely available, and the method is arguably the easiest variation of EMR to perform for small, flat lesions.[7]

In any of the EMR suction-cap methods, even with the new models made of transparent plastic, it is helpful to mark the area of resection using small cautery burns. This allows easier localization of the mucosal target to be suctioned and resected, after injection. EMR appears to be generally safe, with low rates of bleeding and perforation. The risks reported seem to be slightly higher when using suction-cap techniques. Larger saline injections may help make these latter procedures safer.

The great advantage of EMR, compared with mucosal ablation with techniques such as electrocautery, laser, or photodynamic therapy, is the retrieval of a specimen for pathology analysis to assess completeness of the resection. Indeed, EMR was initially designed as a primarily diagnostic technique called "strip biopsy."[5]

In the West, EMR has been used primarily to assist in piecemeal resection of superficially spreading carpet-like colon polyps. Other recent applications have been for elevated, focal areas of high-grade dysplasia and mucosal carcinoma in Barrett's esophagus (generally in patients whose age and comorbid illness preclude surgery).[8] EMR has also been used as a means of debulking nodular or polypoid lesions in such patients before photodynamic therapy (PDT) to the entire Barrett's area.[9]

Photodynamic Therapy

PDT is a 2-part therapy. In the first step, a photosensitizing drug is given and accumulates in the tissue to be treated. Second, the drug is then activated by shining a bright light, usually from a laser, at the target tissue. The activated drug reacts with oxygen in the environment to induce cell death and tissue necrosis. An update and review of PDT was presented by Dr. Kenneth Wang. A great deal has been learned in just a few years regarding the efficacy and safety of PDT in the gastrointestinal tract. Its initial approved use for palliation of advanced esophageal cancer remains valid.[10] Esophageal cancer frequently presents at

an advanced stage with dysphagia, and in this setting, palliative therapy often is appropriate. However, competing therapies, including combined radiation therapy and chemotherapy, expandable metal stents, Nd:YAG laser, and argon plasma coagulator, have decreased the use of PDT for palliation of esophageal cancer.[11]

PDT has potentially much greater importance in the management of mucosal disease. There has been considerable research interest in the use of this technique for high-grade dysplasia in Barrett's esophagus, in the setting of extensive squamous cell dysplasia, and in superficial spreading squamous cell cancer of the esophagus and superficial gastric cancer.[12-19] The other area of interest has been in the palliation of cholangiocarcinoma.[20]

The 2 primary photosensitizers currently in use in gastroenterology have been porfimer sodium (Photofrin) and 5-aminolevulinic acid (5-ALA). Photofrin has been effective in advanced cancer and is being actively tested for high-grade dysplasia and early cancer in Barrett's esophagus. 5-ALA is easier to use and has shorter skin photosensitivity and fewer side effects compared with Photofrin, but treatment effects are very superficial. Laser devices for PDT have improved considerably in recent years with the development of diode lasers with light wavelengths in the correct range and new light guides for improved light delivery (eg, centering balloon devices for long segments of Barrett's esophagus).

Argon Plasma Coagulation

No, it's not a laser, as Dr. Jerome Waye of Mount Sinai Medical Center in New York, who presented this topic, was quick to explain. In this method, originally developed for use in open surgery, argon gas is passed through a coagulation probe with an electrode at its tip. When the electrode is activated by a foot switch, a radiofrequency current passes through the argon beam, which results in an ionized plasma that conducts a spark to the nearest point of tissue contact. The circuit is completed by means of a return electrode plate on the patient.[21]

Since desiccated tissue is resistant to electrical current, the tissue effect of argon plasma coagulation tends to be superficial. However, as Dr. Waye emphasized, deeper injury to the muscularis propria and beyond is possible. In treating areas that have a thinner wall, such as the right colon, Dr. Waye strongly advised decreasing power and gas flow settings to minimize the risk of deep injury and perforation.

Argon plasma coagulation has been used successfully in the treatment of vascular ectasias, radiation proctitis, and flat adenomas.[21] There has been considerable interest as well in treating Barrett's esophagus, but residual Barrett's epithelium beneath new squamous mucosa has been a persistent problem.[22] Recently, the use of higher power and gas flow settings has led to improved eradication but also to more complications, including esophageal strictures.[23]

Endoscopic Ultrasonography

Progress in instrumentation and clinical research continue to expand the potential utility of endoscopic ultrasonography (EUS). This progress was reported by Dr. Charles J. Lightdale from Columbia-Presbyterian Medical Center in New York. He emphasized the development of high-frequency miniprobes that can be passed through the channels of standard endoscopes.[24]

A key rule in ultrasonography is that the higher the frequency of the sound waves used, the greater the

clarity of the images, but the shorter the penetration depth. The new miniprobes at 12, 20, and most recently 30 MHz provide unique images of the wall of the gastrointestinal tract from the esophagus to the rectum.

The ability to image the wall of the gastrointestinal tract as a series of definable layers corresponding to histology, rather than as a single entity, results in a powerful clinical tool and is the basis of many of the indications for EUS. The new miniprobes can be used for evaluation of submucosal lesions, abnormal folds, esophago-gastric varices, and cancer staging. Evaluating areas of dysplasia and early cancer before endoscopic therapy with endoscopic mucosal resection or ablation is an important new indication well suited to miniprobes. New wire-guided probes can be directed into the pancreatic and bile ducts for evaluation of tumors and stones. A new portable receiver from Olympus (EU-M30S) fits on a cart small enough for even the most crowded ERCP (endoscopic retrograde pancreatography) room.[25]

Other indications have emerged stemming from the ability of standard EUS to provide detailed images of areas in immediate proximity to the gastrointestinal tract.[26] In initial clinical trials, EUS appears to be a sensitive method for the diagnosis of chronic pancreatitis.[27] Radial mechanical instruments continue to evolve and improve, as do electronic linear instruments, which can be used to guide needles precisely through the gut wall into surrounding structures.

A relatively new use for EUS-guided fine-needle aspiration is emerging in the staging of non-small-cell lung cancer. Following diagnosis, the disease is usually staged with computed tomography (CT) scan of the chest. Large lymph nodes in the posterior mediastinum and subcarinal areas can now be aspirated for cytologic confirmation of malignancy with EUS guidance. If a lymph node is confirmed to harbor metastases on the contralateral side of the mediastinum from the tumor, the patient will not be cured by surgery alone, and a different management plan must be selected. Thus, a positive EUS-guided cytology can have a major impact on the management of patients with non-small-cell lung cancer. Initial reports put the accuracy of EUS-guided fine-needle aspiration for this purpose in the range of greater than 90%.[28]

New Trends in Endoscopy

A second symposium addressed the major trends that may have an impact on endoscopic practice in the future. Dr. Michael Wallace, from the Medical University of South Carolina in Charleston, saw a new thrust toward making endoscopy more comfortable and acceptable to a wider population with the development of thinner endoscopes. Instruments as small as 5 mm are in current use, and Dr. Wallace and his colleagues have been testing endoscopes as small as 3-4 mm in diameter.

The thinner endoscopes have the potential of being used with topical anesthesia only, avoiding the need for patient sedation. Using these thin instruments, the transnasal route may be preferable in some patients.[29] Dr. Wallace described an inexpensive, portable, instrument 3.1 mm in diameter, without a biopsy channel, designed as a screening tool for Barrett's esophagus in patients with symptoms of esophageal reflux.

Variable Stiffness Colonoscope

Another important development is presently available for colonoscopy: the variable stiffness endoscope. This instrument allows passage through the sigmoid loops with a flexible setting. Stiffness can then be

increased to allow passage through the transverse colon, and around the hepatic flexure to the cecum. The variable stiffness colonoscope seems to offer a major advance in allowing more complete examinations of the colon to be carried out with greater patient comfort.[30,31]

Optical Biopsy

The use of standard biopsy and pathology may also be enhanced or even partly replaced with the development of "optical biopsy." This approach employs new technology related to advances in optical science and computer analysis. For example, light-scattering methods may allow an endoscopist to scan the mucosal surface for dysplasia by analyzing the size of cell nuclei, their arrangement, and their crowding.[32] A view of surface cells in real time may be possible using endoscopic confocal microscopy. Fluorescence spectroscopy is also being studied as a potential means of identifying dysplastic areas.[33]

Optical Coherence Tomography

Endoscopic optical coherence tomography (EOCT) is a new method of imaging that is currently being tested for application in the gastrointestinal tract.[34,35] The method is roughly analogous to EUS, but uses light instead of sound to produce images with a 10-fold greater resolution. In EOCT the path of reflected light is measured using a method called interferometry.

Early studies with prototype systems have produced some striking images of the gastrointestinal mucosa and submucosa, both in vitro and in vivo. Comparison of measurements of architectural layer thickness in EOCT and histology has shown remarkable equivalence.[34,35]

New Endoscopic Surgery

Dr. Anthony N. Kalloo, from the Johns Hopkins Medical Center in Baltimore, Maryland, described his studies testing a method he called "flexible endoscopic surgery." This investigation involved a deliberate perforation of the pig stomach following antibiotic treatment, allowing examination of the peritoneal cavity and liver biopsy using a standard flexible endoscope. The perforation was subsequently closed with endoscopic clips. Dr. Kalloo hopes this method may lead to surgical procedures even less minimally invasive than current laparoscopy, because there will be no skin incisions or puncture sites, thus allowing even more rapid recovery.

Ensuring the Quality of Endoscopy

Dr. Peter Cotton, the session moderator, from the Medical University of South Carolina, was the final presenter. He emphasized 3 trends in the current developments in endoscopy. The first aspect, as discussed by Dr. Wallace, was that endoscopy would become more available, comfortable, and less expensive. Technology, it was emphasized, would also improve diagnostic accuracy. The second drive in this field, the development of endoscopic surgery, as demonstrated by Dr. Kalloo, will further blur the distinction between traditional endoscopy and surgery.

The third trend relates to improved training, practice quality, and accountability. Dr. Cotton saw these developments as necessary and inevitable. Increasing use of reporting software will lead to documentation that is needed for quality assurance. Benchmarking of performance will also become the norm, with computer-generated results.

Concluding Remarks

Web-based learning and the Internet, combined with improved simulation methods, are likely to lead to a revolution in the way that endoscopists learn and maintain their skills. In the end, these developments should surely strengthen gastrointestinal endoscopy as a specialty and directly benefit patients undergoing endoscopic-based procedures.

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New Insights Into Irritable Bowel Syndrome

Kevin W. Olden, MD

Introduction

Irritable bowel syndrome (IBS) is a well-known disorder for both gastroenterologists and primary care physicians. It has been described traditionally as affecting 15% of the North American population. However, the diagnosis of IBS has suffered in the past from a lack of precise diagnostic criteria and difficulties in defining adequate treatment and measuring the impact of that treatment in an effective manner. A number of research and clinical symposia were presented at the Annual Meeting of the American College of Gastroenterology that shed new light on the epidemiology, treatment, and economics of the disease burden of IBS.

The Challenge of Diagnosis

The Rome Criteria

In an attempt to develop standardized diagnostic criteria for clinical practice and research in IBS, international working teams developed the ROME I diagnostic criteria in 1990. In 1999, those criteria were revised and simplified, resulting in the ROME II criteria. Investigators have now begun to evaluate the sensitivity, specificity, and congruence of the ROME II criteria with the ROME I criteria. In one study, Grant Thompson, MD, and colleagues[1] from the University of Ottawa and McMaster University in Ontario, Canada, compared the congruence of both the ROME I and II criteria prospectively in a large population of Canadians. Using standard random telephone polling, the investigators recruited 1149 people, adjusting for demographic variables including age and gender. The prevalence of IBS by ROME II criteria was 12% compared with 13% using the ROME I criteria. When gender was evaluated, the prevalence of IBS was found to be 15% in females and close to 9% in males using ROME II, compared with 18.1% and 18.5% in females and males, respectively, using the ROME I criteria. Investigators concluded that the new ROME II criteria produced similar results when compared with the older ROME I criteria. These findings suggest that the ROME II criteria may indeed provide equal efficacy in identifying patients with IBS while being much simpler to use.

A very different study was presented by M. Zuckerman, MD, from Texas Tech University in El Paso, and G. Nguyen, MD, from Cho Ray Hospital in Ho Chi Minh City, Vietnam.[2] These investigators surveyed 516 predominately healthy Vietnamese healthcare workers and relatives of patients treated at the Cho Ray Hospital. The individuals were surveyed using an instrument that included the ROME I criteria. A total of 233 individuals (42%) responded. A 6% prevalence of IBS was reported in this sample. Five percent of males and 7% of females met the ROME I diagnostic criteria for IBS. Of interest, the gender difference was not significant, putting this study at odds with research done in North America and Europe where the female-to-male ratio in IBS is skewed toward a higher prevalence in women. The investigators concluded that IBS in a Vietnamese population may present different epidemiologic factors, including lower overall presence and less gender variation. This study is important

in that it demonstrates that further epidemiologic studies in populations outside of North America and Europe are needed to better understand the nature of IBS around the world.

Disease Burden

The issue of the disease burden of IBS has been investigated only recently. Previous studies have demonstrated the cost of morbidity due to IBS in the United States to be over $8 billion. To further evaluate the economic burden of IBS, Eisen and colleagues[3] sampled 2354 individuals from large health maintenance organizations in New Mexico. Of the total contacted, 1032 (44%) agreed to participate in a telephone survey. Data collected included demographic characteristics, the presence of a diagnosis of IBS by ROME I criteria, and quality of life measured by the SF-36 questionnaire, a validated general quality-of-life measure and the IBS-QOL, an instrument that is specific for IBS. Patients were screened psychologically with a checklist that measured psychiatric comorbidity and levels of psychosocial distress.

The investigators found that 9% of their sample (94 individuals) met the diagnosis of IBS by the ROME I criteria. There were no demographic differences, including age, gender, race, marital status, education, or income between IBS patients and nonpatient responders. The respondents with IBS were found, on review of their medical records, to have had greater number of outpatient visits in the year preceding the survey compared with non-IBS respondents. However, IBS responders did not differ from non-IBS responders in number of hospitalizations. The patients with IBS tended to use more medications and incurred increased charges for both outpatient visits and prescription drugs. There was also a trend towards higher total costs for all healthcare services for IBS patients during the year that healthcare utilization was measured compared with non-IBS responders. The patients who met the ROME I criteria for IBS had significantly lower scores on the SF-36 compared with non-IBS responders ($P < .0001$).

The investigators concluded that using a cohort of patients in a managed care organization where healthcare utilization and costs could be tracked easily demonstrated that IBS sufferers had significantly more outpatient visits and use of prescription medications than patients without IBS. Further, IBS patients experienced decreased levels of health-related quality of life as opposed to non-IBS respondents. The investigators believed that these findings demonstrated a significant disease burden for IBS.

Levy and colleagues[4] presented a similar study that was performed at a large health maintenance organization (HMO) in the Puget Sound area of Washington State. These investigators performed a retrospective study of patients who had been diagnosed with IBS. The medical records of 3153 patients who were diagnosed with IBS were examined and compared with 3153 age- and gender-matched controls from the same HMO who were not diagnosed with IBS and an additional 3153 individuals who were also age- and gender-matched who presented for routine checkups and new medical complaints. Cost of overall care and GI-related costs of care were measured for a 3-year period. The investigators found that for the index year of diagnosis, the total cost of care for IBS patients was $4044, or $1415 higher than for controls. In addition, the IBS patients continued to have healthcare utilization costs approximately $1000 more per person than in the 2 subsequent years of tracking after the initial diagnosis was made.

When GI-related care was specifically measured, the IBS group consumed $582 in the index year; that was reduced to some degree in the 2 subsequent years after diagnosis. The largest components of GI-related costs in the first year of the IBS diagnosis were primary care visits ($178), medications

($108), outpatient procedures ($98), radiographic procedures ($77), and specialists' visits ($64). Of interest, there were no significant differences in the number of emergency department visits, inpatient care, or laboratory tests between IBS and non-IBS patients. When all medical problems in both the IBS patients and controls were examined, it was found that less than half of the difference in costs was explained by the cost of IBS-related care. The investigators concluded that IBS indeed had a greater cost-of-care burden, particularly in the first year of diagnosis.

Innovations in Treatment

Significant advances in the treatment of IBS have been evolving over the last few years. The increase in our understanding of the enteric nervous system and the importance of neurotransmitters present in the gut have been described by various investigators. These findings, in turn, have led to an explosion in research to develop specific agents that can positively affect neurotransmitter function in the treatment of IBS patients.

Consequently, the American College of Gastroenterology sponsored a symposium on the treatment of IBS, which was moderated by Drs. Kevin Olden and Arnold Wald.[5] The symposium addressed the difficulties of designing valid clinical trials for IBS and identified the psychosocial and gender factors associated with treatment response as well as the psychiatric and psychological comorbidity that can influence a patient's behavior and treatment response. The use of antidepressant medications and active agents now being developed and entering clinical practice were all discussed in detail.

The Difficulties in Designing Clinical Trials

Dr. Nicholas Talley[5] from the University of Sydney, Australia, began the symposium by outlining the difficulties associated with performing high-quality clinical trials for any therapeutic approaches to IBS and the methodologic deficiencies of trials published over the last 30 years (including issues of patient recruitment, lack of standardized diagnostic criteria, lack of controls, inadequate consideration to the high placebo response rate seen in IBS, and inadequate outcome measures). Dr. Talley concluded that over these last 3 decades, we have yet to produce a clinical trial that meets the "gold standard." Nor was there any one trial that we could point to and declare unequivocally the efficacy of any particular treatment approach. The absolute importance of maximizing methodologic quality in testing any proposed treatment for IBS was emphasized, lest erroneous or inaccurate conclusions be drawn. Important to further emphasize is that this literature, although advancing quite rapidly, is still immature and thus there are additional lessons to be learned in planning the "ideal" IBS clinical trial.

The Role of Psychosocial and Hereditary Factors

Dr. Rona Levy[5] from the University of Washington focused on recent research on family dynamics and heredity as they influence IBS expression in patients. In her research, Dr. Levy found that patients with IBS were slightly more likely to have children who would also develop IBS. However, Dr. Levy was quick to emphasize that the reasons for this association remain unclear. Whether this finding represents a genetic phenomenon, as proposed by some investigators, or socialization, family dynamics, or learned healthcare behavior needs to be further determined. Identifying these issues has important treatment implications because there may be a strong level of concern and anxiety within a family about the significance of IBS and its effect on that family that in turn, can influence patient behavior.

Data were also presented demonstrating that women have a tendency to respond differently from men to visceral pain, which in turn may influence response to drug treatment. The importance of designing trials adequately balanced between men and women and paying attention to gender-based response differences is clearly important for generating high-quality data on drug and other interventions for IBS.

Psychologic Comorbidity

Dr. Arnold Wald from the University of Pittsburgh Medical Center reviewed the prevalence of psychiatric comorbidity in patients with IBS.[5] Dr. Wald discussed well-established data showing the high prevalence of anxiety disorders, particularly panic disorder, mood disorders, and somatization disorder in patients with IBS. It should be emphasized that IBS is not a psychological disorder and does not represent "a form fruste" of a psychiatric disorder. Rather, it is important to understand psychiatric disorders as comorbid conditions that can influence presentation, healthcare seeking, drug response, and prognosis. Using case studies, Dr. Wald presented psychiatric-disorder patients from his practice who, at first view, would seem to have IBS. Likewise, he presented patients with IBS who, although distressed, did not have a diagnosable psychiatric disorder on further investigation but who could have easily been misperceived as having one.

Dr. Wald presented illustrative cases to demonstrate the importance of taking an adequate history and the utility of office-based psychological screening instruments for identification of psychological issues. Dr. Wald stressed the ease of using these screening instruments in this setting, their applicability to office-based practice, and how to present them to the patient in a positive and helpful manner.

The Role of Antidepressants*

The use of antidepressants in IBS was discussed by Kevin Olden, MD, of the Mayo Clinic in Scottsdale, Arizona.[5] Dr. Olden reviewed the history of antidepressants in gastroenterology. Specifically, the anticholinergic properties of the older tricyclic antidepressants and their presumed effect on GI motility and the usefulness of tricyclic antidepressants in the treatment of neuropathic nongastrointestinal pain syndrome, such as peripheral neuropathy, were addressed. Dr. Olden also described the effect of neurotransmitter systems found in the gut. He reviewed clinical trials, particularly those by Greenbaum, Cannon, and Clouse, that investigated the use of desipramine,* imipramine,* and trazodone,* respectively, for treating functional gastrointestinal disorders.

Dr. Olden emphasized the commonality of the findings of these separate trials using 3 different antidepressants. In all of them, the subjects had no significant demonstrable changes in gastrointestinal motility nor any significant changes in their psychiatric status as a result of the antidepressant intervention. However, the patients did have significant improvement in their GI symptom ratings as well as -- most important -- significant improvement in their overall sense of well being. Dr. Olden emphasized that these findings suggest a site of action of antidepressants both in the gut as well as in the central nervous system where the sensations produced in the gut by IBS are processed and modulated to produce the patient's "report" of his or her symptoms. Patients can begin on low doses of these antidepressants and are less likely to experience troublesome side effects. Dr. Olden stressed the importance of understanding that these drugs, when used in the setting of IBS, are an "off-label" indication, and, therefore, physicians should proceed with caution and ensure their patients' understanding of the reasons for their use.

Finally, Dr. Olden reviewed the opportunities that are emerging for the use of antidepressants in gastroenterologic practice. The development of an ever increasing number of new antidepressive agents, including the selective serotonin reuptake inhibitors (SSRIs) and agents that tend to have lower side effect profiles, all deserve further study in GI practice to help define their role in treating IBS and other functional gastrointestinal disorders (such as functional dyspepsia, esophageal dysmotility, and functional abdominal pain).

The Role of Serotonin

The session was concluded by Dr. Lin Chang from the UCLA School of Medicine, who addressed the use of newer serotonergically active agents for IBS. Dr. Chang reviewed the significance of serotonin as a target neurotransmitter in the therapeutic intervention of the functional gastrointestinal disorders. She emphasized that 95% of serotonin contained in the body is located in the gastrointestinal tract, with the extraneous 5% being primarily located within the brain.

Dr. Chang presented the latest data on alosetron (*Lotronex*), a $5HT_3$ antagonist and a significant inhibitor of gastrointestinal motility. This inhibitive property makes alosetron an ideal agent for the treatment of diarrhea-predominant IBS. Dr. Chang also discussed the clinical data supporting the efficacy of alosetron in reducing stool frequency in patients with diarrhea-predominant IBS and its ability to decrease abdominal pain and rectal urgency. Other properties of the drug include a lack of adverse interactions, the need for dose adjustment with age, and the absence of metabolic changes in patients with renal or liver dysfunction. Because of its significant antiprokinetic effect, alosetron can commonly produce constipation, which occasionally can be severe. It is important for the physician to be proactive in treating constipation early if seen in these patients.

Dr. Chang also presented data on agents still in development, including tegaserod and prucalopride, both of which act on $5HT_4$ receptor sites. These drugs are being developed specifically for the treatment of constipation-predominant IBS because of their prokinetic effect. Preliminary data published to date studying the effect of tegaserod on gastrointestinal transit and its ability to decrease bloating and abdominal pain in patients with constipation-predominant IBS appear promising.

Additional Studies and Strategies for IBS

Drotaverine

In addition to this symposium on the treatment of IBS, a number of clinically relevant research abstracts were presented. Misra and colleagues[6] from the University of New Delhi Medical School in India presented the results of a randomized double-blind, placebo-controlled trial of drotaverine for the treatment of IBS. Drotaverine is a selective inhibitor of phosphodiesterase isoenzyme IV, which has been found useful in smooth muscle motility disorders. Seventy consecutive patients between the ages of 18 and 60 diagnosed with IBS using their own criteria were studied in this prospective trial. Patients were treated with drotaverine 80 mg 3 times a day and compared with placebo during a 4-week trial and an additional 4-week follow-up period. These investigators found that drotaverine significantly reduced pain compared with placebo ($P < .001$). Pain severity scores also increased significantly in the drotaverine group compared with placebo ($P < .001$). Patients treated with drotaverine also experienced significant improvement in global relief of abdominal pain, again compared with placebo ($P < .001$), and significant

improvement in stool frequency ($P < .001$). No adverse effects were observed in any of the patients either in the placebo or treatment groups. The study authors concluded that drotaverine produced significant global improvement in abdominal pain in patients with IBS.

Alosetron

Recently, the 5-HT_3 antagonist alosetron was approved by the FDA for the treatment of diarrhea-predominant IBS in women. And, in the wake of this, a number of new studies were presented. Jhingran and colleagues[7] studied patient satisfaction in individuals with nonconstipated IBS treated with alosetron. A total of 801 women were studied using a 12-week randomized, double-blind, placebo-controlled multicenter trial of alosetron 1 mg twice daily. These investigators found that overall satisfaction in those patients treated with alosetron was significantly higher than in the placebo group ($P < .001$). On entry into the trial, less than 10% of all subjects reported that they were either satisfied or extremely satisfied with their previous IBS treatment regimens. In contrast, at the conclusion of the alosetron trial, 12 (69%) of the subjects treated with alosetron reported that they were either satisfied or extremely satisfied with treatment compared with only 42% of the controls ($P < .001$). They also found a high correlation between overall patient satisfaction as well as satisfactory control of rectal urgency and global improvement of all IBS symptoms. Constipation was the only adverse event reported significantly more frequently in the treatment group (39% vs 14% of controls). The study authors concluded that above and beyond standard outcome measures such as decreased pain and change in bowel movements, patients treated with alosetron also experienced high levels of satisfaction with their care.

In a related study, Markowits and colleagues[8] studied the efficacy of alosetron in patients with rectal urgency. Over 800 patients were studied in a 12-week randomized, double-blind, placebo-controlled multicenter trial of the efficacy and tolerability of alosetron 1 mg twice a day. (During the screening period, subjects had reported a lack of satisfaction with control of their symptoms of bowel and rectal urgency at least 50% of the time.) This factor was followed throughout the course of the clinical trial over 12 weeks. The study authors found that patients treated with alosetron were significantly more likely to report improvement in rectal or bowel urgency ($P < .001$). There was a high correlation seen between improvement in global well-being and satisfactory control of rectal urgency at week 12 ($r = 0.54$). The investigators concluded that alosetron selectively improved control of rectal urgency in the context of global improvement of IBS symptoms compared with placebo.

[Ed. note: Recently the FDA announced the development of a medication guide (FDA-approved patient labeling) to help ensure that women using the prescription drug alosetron hydrochloride for treatment of the diarrhea-predominant form of IBS will understand the rare but serious risks of this drug and how they can recognize those risks and take early action to prevent serious harm. These risks include complications from constipation and the risk of ischemic colitis, which is caused by reduced blood flow to the intestines.]

Acupuncture?

Lu and colleagues[9] discussed the use of acupuncture, investigated in a randomized, controlled trial of 27 patients with IBS diagnosed by their own criteria and assigned to receive acupuncture treatment or relaxation sessions. Using a crossover design method, the subjects received both modalities. In addition to demographic information and specific IBS symptoms reported, patients also rated their overall quality

of life on entry to and exit from the study. The study authors treated the patients with acupuncture or relaxation sessions 3 times a week for a period of 2 weeks. A follow-up observation run was then performed for 4 weeks.

These investigators found that patients' quality-of-life and gastrointestinal symptom scores were improved equally in the 23 who completed both the acupuncture trial and the relaxation sessions. A statistically significant reduction in abdominal pain was observed in both groups at the end of the trial. However, when the patients were followed for the 4-week period posttrial, only in the acupuncture group did pain reduction persist ($P < .05$). Furthermore, a significant reduction in stress perception was also observed in the acupuncture group, but not in the relaxation group ($P < .05$). It was concluded that acupuncture appears to be an effective modality in the treatment of IBS, particularly for pain and disease-related stress, and exceeds standard relaxation treatment. This intriguing finding is of particular interest because of the increasing attention paid to so-called alternative treatments for IBS by patients and the medical community itself. Additional studies will be needed to confirm these results. The work of Lu and colleagues, however, is an important step in this direction. Clearly, acupuncture as well as other alternative modalities deserve additional study in this disease setting.

Conclusion

Irritable bowel syndrome continues to pose a significant challenge to the physician in terms of both diagnosis and management. The material presented during these meeting proceedings serves to underscore not only the progress that has been made in recognizing this disease entity (eg, establishment of the Rome Criteria), but also the promise of new therapeutic interventions (eg, tegaserod) that are waiting in the wings.

**** The United States Food and Drug Administration has not approved this medication for this use.***

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Barrett's Esophagus: The Challenge Continues

M. Brian Fennerty, MD

Barrett's Esophagus: Why All the Interest?

For over a decade, adenocarcinoma of the esophagus has been recognized as the most rapidly rising incident tumor of any cancer in the United States and Western Europe. In the year 2000, esophageal cancer will result in nearly 12,000 deaths in the United States alone, with the majority being adenocarcinoma that arises from its precursor lesion, Barrett's esophagus (BE). Despite extensive research interest in this disease, many questions remain regarding the pathogenesis, incidence and prevalence, natural history, effectiveness of currently recommended screening and surveillance strategies, and therapeutic approach to BE. This article discusses the latest data on BE as reported in abstracts and educational symposia presented at this year's Annual Meeting of the American College of Gastroenterology.

Can We Identify the Patient at Risk of Having BE?

Chronic symptoms of gastroesophageal reflux disease (GERD) occur in 20% of adult Americans and 10% to 15% of adults with chronic GERD will have BE. The characteristics of the chronic refluxer that determine who will and will not develop BE are as yet undetermined. Because of this inability to predict risk, current recommendations are to screen for BE in all patients with GERD symptoms of greater than 5 years' duration. This recommended practice management strategy necessitates that 85% or more of reflux patients without BE undergo a costly and invasive endoscopic procedure. Ideally, if clinical factors could be identified that differentiated risk for BE, then a more effective clinical and economic screening strategy could be devised.

Avidan and colleagues[1] from the VA Medical Centers in Albuquerque, New Mexico, and Hines, Illinois, performed a case-control study aimed at identifying potential risk factors for BE in reflux patients. Additionally, they sought to determine risk factors for length of Barrett's because many investigators believe columnar length correlates with cancer risk. In the study, 256 GERD patients with BE were compared with 229 GERD patients with nonerosive reflux disease. All cases and controls had undergone endoscopy, manometry, and ambulatory intraesophageal pH monitoring. Patients with BE were found to have more frequent reflux, were more likely to have a hiatal hernia (76% vs 36%), be white (96% vs 85%), and smoke (87% vs 76%). Frequency of reflux, hiatal hernia, smoking, alcohol use, and the magnitude of intraesophageal acid exposure were also identified as being associated with a greater length of BE. Based upon these findings, the investigators concluded that BE was associated with clinical factors indicating more severe reflux disease.

These clinical, endoscopic, and pH data correlate with a recent case-control study of the association between esophageal adenocarcinoma and more frequent, severe, and longer-duration reflux symptoms. Thus, more severe GERD, either based on symptoms or objective testing by endoscopy or pH monitoring, is indicative of an increased risk of having BE. Whether a discriminating predictive tool can be developed from data such as these in order to assist the clinician in determining who should be screened is unknown, but there does appear to be some potential for such an instrument.

Once We Diagnose BE, What Do We Do?

Once a patient is determined to have BE, current recommendations and the standard of care in most communities dictate performing periodic endoscopic surveillance exams in an effort to identify incident neoplasia at an early, treatable, and curable stage. The benefit of such surveillance strategies remains unproven and the ideal timing, technique, and marker of cancer risk is unknown. At this time, the marker indicating the greatest cancer risk has been the identification of high-grade dysplasia (HGD). The following 2 studies address the issues regarding knowledge and adherence of current practice guidelines for BE and investigate the use of a novel marker of cancer risk.

Adherence to Practice Guidelines

In 1998, the American College of Gastroenterology published a practice guideline on BE. These guidelines were also endorsed by the American Gastroenterological Society and the American Society for Gastrointestinal Endoscopy. This guideline was based on the best available evidence at that time and, where evidence was lacking, on consensus expert opinion. Cruz-Correa and associates[2] from The Johns Hopkins University investigated gastroenterologists' awareness and adherence to these guidelines and also identified factors associated with adherence to these recommendations.

In this prospective study, a survey questionnaire consisting of 3 case scenarios was administered before publication of the guideline and again 18 months later. Sixty-five percent of those sent the survey responded, and only 65% of those gastroenterologists were aware that the guidelines existed. Somewhat surprising, awareness was not associated with adherence to the guidelines. Overall adherence increased from 27% to 38% (P = .04) and adherence for nondysplastic BE increased from 72% to 81% (P = .03), but there was no change in adherence for dysplastic BE, either before or after publication of the guidelines. Adherence was less likely in a fee-for-service environment and among older gastroenterologists. Based upon these data, it was concluded that awareness of the guidelines was

insufficient and that adherence was based on a physician's agreement with the recommendations. It was also believed that the major barrier to adherence included insufficient data supporting the recommendations. I would conclude that additional work needs to be done to justify and confirm the effect of these guidelines. However, these data also suggest that financial incentives in a fee-for-service environment and the lack of continuing education in older physicians are other important barriers that must be quickly overcome.

Markers of Cancer Risk

In patients with BE undergoing endoscopic surveillance exams, HGD found on mucosal biopsy is the currently accepted gold standard for cancer risk. However, HGD may not be the optimal marker because it is subject to inter- and intraobserver error and may be missed with routine endoscopic biopsy. Additionally, unrecognized cancer is found to coexist in only 25% to 40% of patients with HGD and the incidence of cancer is less than 50% over 5 years. Many other markers of cancer risk, including flow cytometric abnormalities and p53 mutation, among others, have also been evaluated as either substitutes for HGD or as adjunctive tests to HGD.

Barrett's esophagus is defined as the presence of intestinal metaplasia within the tubular esophagus. Intestinal metaplasia is characterized by the presence of goblet cells and occasionally noted Paneth cells. Human defensin 5 (HD5) is expressed in Paneth cells. Shen and colleagues[3] from the Cleveland Clinic sought to determine whether HD5 could be used to identify BE and/or correlate with the presence or absence of neoplasia within BE. Using a novel monoclonal antibody to HD5, histochemical techniques were used to demonstrate that normal squamous mucosa did not have HD5 expression, whereas HD5 was increasingly expressed as Barrett's mucosa as it progressed from dysplasia to cancer. The location of HD5 expression also correlated with whether dysplasia or cancer was present with HGD and cancer expressing HD5 on the surface as well as the glands. It was concluded that HD5 might be another useful marker of neoplasia in the setting of BE.

I would emphasize that further efforts such as this are needed to determine the optimal marker of cancer risk. However, at this time the presence of HGD remains the gold standard for cancer risk in this population of patients.

Is There Evidence That We Can Eliminate Cancer Risk, or BE Itself, With Endoscopic, Surgical, or Pharmacologic Therapies?

Symptoms of GERD in patients with BE can be effectively eliminated with surgical or pharmacologic antireflux therapies. However, regression of BE does not occur with these interventions alone. Because of the inability to effect regression of Barrett's mucosa with antireflux therapies, secondary prevention of cancer through chemoprevention and/or endoscopic elimination of Barrett's from the esophagus is being actively investigated. For example, abnormal proliferation and differentiation in BE is normalized by elimination of pathologic intraesophageal acid exposure. Additionally, it has been demonstrated that endoscopic injury to the esophagus applied thermally or chemically in conjunction with antireflux therapy can cause endoscopic reversal of BE. However, neither of these approaches has been shown to eliminate cancer risk or the need for continued surveillance.

Is Control of Reflux Sufficient?

Carlson and colleagues[4] from Cleveland, Ohio; Tucson, Arizona; and Houston, Texas, sought to determine whether potent antisecretory therapy with a proton pump inhibitor (PPI) in patients with BE altered malignant progression in those already exhibiting genomic instability, as measured by p53 mutation. Six patients with p53 mutation and 7 patients without this mutation were followed for a mean of 5 years. Two of 3 patients with the mutation developed incident dysplasia over that time vs none of those without the mutation. In patients with p53 mutation, DNA ploidy abnormality persisted or developed in 83% vs 43% of those without p53 mutation. These findings showed that aggressive antisecretory therapy failed to halt progression of neoplasia in patients who had already developed a defect in a DNA repair gene.

I interpret these data to indicate that control of reflux will be unlikely to influence carcinogenesis if applied late in the process, but that this does not rule out the possibility of using acid suppression as a chemopreventive strategy earlier in the process. Perhaps reversal is not a necessary endpoint of therapy, and what we may need is simply early enough intervention with antisecretory drugs. This concept will require confirmation in a carefully designed clinical trial, determining outcome of this approach.

Reversal of BE

There has also been intense interest in using endoscopic techniques combined with antisecretory therapy to reverse BE. The optimal technique(s) and outcomes of these therapies is as yet unknown. All of the described endoscopic approaches have been performed in conjunction with either pharmacologic or surgical antisecretory therapy. Whether normalization of intraesophageal acid exposure is required for these techniques to be successful is not known.

Sampliner and coworkers[5] from the University of Arizona used pH monitoring data to correlate the outcome of endoscopic reversal using multipolar electrocoagulation (MPEC) therapy to esophageal acid exposure. Patients were administered 40 mg omeprazole twice daily and pH monitoring was performed prior to the endoscopic therapy. Three of 20 patients continued to have abnormal intraesophageal acid exposure despite this high-dose PPI therapy, and all had successful endoscopic and histologic reversal. Three of the remaining 17 patients with normal esophageal acid exposure had continued evidence of BE after therapy.

These data indicate that normalization of intraesophageal acid exposure is not a prerequisite to endoscopic elimination of BE. However, the lowest effective dose allowing reversal is not known and will require further study.

What Happens to Patients With HGD When Treated by One of These Endoscopic Reversal Techniques?

Photodynamic therapy (PDT), argon plasma coagulation (APC), laser, MPEC, and other endoscopic techniques have been used to manage BE patients with and without dysplasia. In patients with HGD who are either unable to have surgery or refuse to have surgery, PDT is the only technique for which there are sufficient data to suggest a possible therapeutic effect. Sharma and colleagues[6] from the University of Kansas and the University of Arizona reported on 8 patients with HGD treated with a combination of Nd:YAG laser and MPEC thermal therapy. At most recent follow-up, 3 had no residual BE, 1 had nondysplastic Barrett's, 3 had low-grade dysplasia only, and 1 had persistent HGD. This technique, which is more widely available than PDT, may become a reasonable alternative in this patient

population.

In Patients With Heartburn or BE, What Is the "Real" Risk of Developing Esophageal Adenocarcinoma?

We have been hampered in our understanding of the natural history of BE because of insufficient data on which to analyze risk. The limited data that have been available are either contradictory or subject to various interpretations. In an effort to assess what is known about cancer risk in patients with either heartburn or BE, Walter Peterson, MD, Professor of Medicine at the University of Texas, Southwestern, and Philip Schoenfeld, MD, Associate Professor of Medicine at the University of Michigan, co-chaired a symposium addressing these issues.[7]

The symposium was based on 2 focused questions in evidence-based medicine (EBM):

1. Among patients with heartburn occurring daily for 6 or more years, what is the likelihood of developing esophageal adenocarcinoma?
2. Among patients with BE, what is the likelihood of developing esophageal adenocarcinoma 5 and 10 years after the diagnosis of BE?

Dr. Schoenfeld discussed the methodology of EBM in a critical appraisal of a study investigating harm. Methodology, validity, the results (odds ratios and relative risk), and how to determine whether the results can be applied to a specific patient were discussed as an overview.

Hashem El-Serag, MD, Assistant Professor of Medicine at Baylor University, discussed an epidemiologic investigation conducted by Lagergren and colleagues[8] of the possible association between gastroesophageal reflux (frequency, duration, and severity) and esophageal adenocarcinomas. Based on data presented, the overall conclusion was that there was good evidence and probably a causal relationship between GERD and this cancer. Thus, the more frequent, the more severe, and the longer the period of reflux symptoms, the greater the risk for esophageal adenocarcinoma.

Prateek Sharma, MD, Assistant Professor of Medicine at the University of Kansas, analyzed the literature regarding incidence of cancer in patients with BE. Using 2 inception cohort studies from the University of Arizona and the Cleveland Clinic,[9,10] he concluded that the incidence of adenocarcinoma in these patients was between 0.4% and 0.5% per year.

Richard Sampliner, MD, Professor of Medicine at the University of Arizona, continued the trend by addressing our current EBM knowledge of BE and what is lacking.[7] The consensus was that, unfortunately, very little is known outside of those data discussed above. While it is clear that the risk of adenocarcinoma is increased dramatically in patients with BE or heartburn, the overall incidence of this cancer remains low in this population. Whether the rates are sufficient to justify currently recommended screening and surveillance strategies cannot be determined from our present knowledge base. Well-designed clinical trials will be needed to answer this and other clinically important questions regarding this disease entity.

Summary

The material discussed during these proceedings underscores the significant deficits in the information upon which to base clinical decision making in patients with BE. It further emphasizes the importance of additional research regarding this clinically important disease. Hopefully, new data arising during the next several years will enable us to stratify risk and confirm the effectiveness of therapy in these patients.

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Chronic Hepatitis C

Rowen K. Zetterman, MD, FACP, FACG

Introduction

Chronic hepatitis C represents a significant public health challenge in the United States. Approximately 4 million Americans are infected with the hepatitis C virus (HCV), and an additional 35,000 new cases occur each year. Only 15% of patients who become infected appear to spontaneously clear the virus, meaning that approximately 85% of infected individuals will develop chronic viral hepatitis C.

Reflecting the urgency of this growing problem in healthcare, a number of research and clinical symposia held at the Annual Meeting of the American College of Gastroenterology focused on the epidemiology, clinical features, and medical management of chronic hepatitis C.

Epidemiology

Dr. Mitchell Shiffman of the Medical College of Virginia, introduced a clinical symposium by establishing that approximately 1.8% of the American population is infected with HCV, with African Americans about 2 times more likely to be infected than whites. The peak prevalence of chronic hepatitis C is in the fourth and fifth decades of life, with men more likely to be infected than women.

Screening

The most commonly used screening test is the ELISA II study for detecting antibody to HCV (anti-HCV). While the recombinant immunoblot assay (RIBA test) has been used in the past to confirm the likelihood of HCV disease, measurement of circulating HCV RNA is often most helpful in confirming HCV infection, especially in those with normal aminotransferase levels, those who lack risk factors for infection, and in those with other liver diseases (such as autoimmune hepatitis), where both the antinuclear antibody (ANA) and anti-HCV may be present. Measurement of HCV RNA is also indicated for monitoring treatment response during therapy. Dr. Shiffman noted that the titer of HCV RNA remains fairly constant during HCV infection in most patients. HCV RNA titer does not appear to be related to histologic severity of the associated liver disease. There are several genotypes of HCV. Approximately 70% of HCV-infected individuals in the United States are infected with genotype 1 (ie, 1a or 1b). This genotype is typically more resistant to conventional interferon-ribavirin therapy than are HCV genotypes 2 or 3.

Disease Progression

Among those individuals infected with HCV, at least 20% will develop progressive liver disease and, ultimately, cirrhosis. Other concomitant risk factors such as ethanol consumption will increase the likelihood of developing cirrhosis, and therefore, all patients who are anti-HCV positive should be strongly encouraged to avoid alcohol. Of those individuals who go on to develop cirrhosis, approximately 50% will show signs of decompensation (eg, ascites, coagulopathy, or encephalopathy) within 5-10 years.

While many individuals with HCV infection are asymptomatic, depression appears to be common. When quality-of-life measurements are used, the patient with known HCV infection shows an overall reduction in score.

While hepatic histology remains the gold standard for determination of cirrhosis in HCV-infected

individuals, Mark Cumings and colleagues[1] of Walter Reed Army Medical Center in Washington, DC, presented a poster that showed that patients with a concomitantly elevated serum alkaline phosphatase were 5.7 times more likely to have cirrhosis than those whose alkaline phosphatase levels were not increased. The study authors evaluated more than 500 patients who were HCV-RNA-positive by studying both serum alkaline phosphatase and aminotransferase levels. The ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) was also determined. As noted, those patients with an elevated alkaline phosphatase were more likely to have coexisting cirrhosis. An AST/ALT ratio greater than 1 was observed in 17% of patients and this was also indicative of more significant underlying histologic disease.

Screening for Hepatocellular Carcinoma

Patients who are infected with HCV have an increased risk of developing hepatocellular carcinoma (HCC) when compared with uninfected individuals. In a breakfast session held at the Annual Meeting of the American College of Gastroenterology, Dr. Robert S. Brown from the Columbia University College of Physicians and Surgeons, in New York,[2] reported that the annual incidence of HCC in patients with chronic hepatitis C and cirrhosis could be as high as 5%. In a related poster presentation, Dr. Birdi and colleagues[3] of the Louisiana State University Health Sciences Center, in New Orleans, also suggested that the combination of HCV and hepatitis B virus (HBV) infection may be more likely to result in development of HCC as well, and that this factor could explain the increased risk for this malignancy in African Americans. In a population of 39 patients with HCC in whom both HCV and HBV testing was done, 36% of African Americans were positive for both viruses, while only 7% of whites were similarly coinfected. Although this is a small study, it does raise an interesting question that can be further evaluated with larger patient cohorts that have both HCV and HBV coinfection.

How should HCV-infected patients who also have cirrhosis be screened? To help answer this question, Dr. O.S. Lin and colleagues[4] of Stanford University in Palo Alto, California, presented a Markov decision analysis model of patients with HCV-related cirrhosis to determine the cost-effectiveness of screening with transabdominal ultrasound and serum alpha-fetoprotein (AFP). The study authors compared abdominal ultrasound and AFP testing at 6 monthly intervals to ultrasound every 12 months vs no screening, in a model population of 40 year-old, HCV-infected individuals with Child's class A cirrhosis. Screening was found to be most cost-effective when compared with no screening, when hepatic ultrasounds were done at 12 monthly intervals. Screening every 6 months, however, had the most expected gain in quality life-years for those who developed HCC. The cost-effectiveness of annual hepatic ultrasounds and AFP screening was approximately $31,000 per quality-adjusted life-year gained. I believe these data suggest that the practice of annual ultrasound evaluation of the liver with annual or semi-annual AFP measurement is a reasonable approach to screening those persons at risk for HCC who are infected with HCV and have cirrhosis.

Treatment of HCV Infection

Combination Interferon/Ribavirin Therapy

In a clinical symposium addressing management issues in HCV, Dr. Michael Fried[5] indicated that the combination of interferon-alpha with ribavirin represents the current recommended therapeutic strategy for patients with HCV infection. A sustained response of approximately 38% overall for loss of HCV

RNA was reported previously for the US trial of interferon/ribavirin combination therapy. When the American and European trials are combined, those patients with HCV genotypes 2 and 3 do better with combination interferon and ribavirin, with approximately two thirds clearing virus vs only about one quarter of those with genotype HCV1. Furthermore, patients with genotypes 2 and 3 only require 6 months of therapy to produce a sustained response, whereas those with genotype 1 should receive 1 year of therapy. For patients with HCV genotype 1 who still have abnormal liver tests and HCV viremia after 6 months of therapy, therapy can be stopped because it is unlikely that continued treatment will result in clearance of the virus.

Should Patients With Normal Liver Function Tests Be Treated With Combination Therapy?

Whether patients with HCV infection who have normal liver tests should be treated with combination interferon/ribavirin remains controversial. Data reported from previous trials of interferon monotherapy in patients with chronic HCV infection and normal liver tests have raised some concern about worsening liver disease in nonresponders. Dr. Hassanein and colleagues[6] from the University of California in San Diego, evaluated combination therapy with interferon and ribavirin in 20 patients with normal aminotransferases, some of whom had induction therapy with higher-dose interferon. In this study, patients with normal liver tests had similar response rates to those reported in previously published studies of those with abnormal liver tests. In addition, there was a further reduction in the serum ALT values with treatment in patients with normal aminotransferase levels. As reported in other studies, these investigators also noted that those with normal liver tests tended to have milder histologic disease at biopsy before treatment.

In a related poster session, Dr. Pena and colleagues[7] from Albert Einstein Medical Center in Philadelphia, Pennsylvania, presented data on 28 patients with normal liver tests and HCV infection. Patients with normal aminotransferase levels appeared to have an increased treatment response at the end of treatment, but did not show any difference in sustained response over those whose pretreatment aminotransferases were elevated. These studies further suggest that combination therapy can be given to those with HCV infection and normal liver tests. However, some investigators still believe that large clinical trials should be completed before making combination therapy with interferon/ribavirin for those with normal liver tests and HCV infection the standard of practice.

Can the HCV Patient With Compensated Cirrhosis Be Treated?

Data from previous studies of interferon monotherapy have suggested that although patients with compensated cirrhosis from HCV can be treated, they will have a reduced response to treatment. Dr. Pereyra and colleagues[8] from Albert Einstein Medical Center in Philadelphia enrolled 23 patients with cirrhosis in a combination interferon/ribavirin treatment trial and compared their outcome with 67 patients without cirrhosis. All patients had previously failed sustained response to interferon monotherapy. The patient demographics, viral levels, and HCV genotype distribution was similar among both groups. These investigators did not find a difference in response rates between patients with cirrhosis vs patients without cirrhosis. These data are in concert with current recommendations that treatment with combination interferon and ribavirin is indicated for patients with compensated cirrhosis from HCV.

The Role of Induction Therapy

What is the role of induction therapy in patients infected with HCV? Should patients be initially treated with higher-dose interferon prior to standard therapy with interferon-alpha 3 million units subcutaneously 3 times/week and oral ribavirin at either 1000 or 1200 mg/day? Will such a strategy result in improvement of sustained response?

Dr. A.S. Bhatia and colleagues[9] from the Medical College of Virginia evaluated high-dose interferon therapy in 86 patients and compared the outcome with 95 patients treated with the standard regimen. Those receiving high-dose therapy received 5 million units of interferon-alpha-2b daily for 1 month, followed by 5 million units interferon-alpha 2b plus ribavirin 1000-1200 mg/day for 1 month, then 5 million units interferon-alpha 3 times/week plus daily ribavirin for 1 month, and then 9 months of standard therapy. Approximately one quarter of the patients in both groups were dropped from the study due to side effects of treatment. At 1 year, there was no difference in virologic response between patients treated with high-dose induction therapy and those treated with standard therapy. African American patients, patients with nongenotype 1, and those with an HCV viral load of greater than 2 million copies of virus/mL prior to treatment were less likely to respond to therapy.

In a similar study, Dr. M. Sjogren and colleagues[10] reported that induction with interferon-alpha 2b 5 million units subcutaneously daily for 4 weeks followed by standard interferon/ribavirin therapy did not improve treatment response rates over initial standard interferon/ribavirin therapy alone. These data indicate that induction with high-dose interferon prior to standard treatment will not improve overall response in HCV therapy.

Side Effects of Combination Therapy

Combination therapy with interferon and ribavirin is associated with some adverse effects. Interferon, for example, is linked to thyroid dysfunction.

In this setting, Dr. G. Surla and colleagues[11] from New York-Presbyterian Hospital identified 13 patients (8 women, 5 men; average age = 47 years) with thyroid disease following interferon therapy. Thyroid disease was first recognized 5.3 months following initiation of therapy. Four patients had hyperthyroidism and 9 patients developed hypothyroidism; 5 of these patients had transient hyperthyroidism before becoming hypothyroid. Thyroid autoantibodies were present in 5 patients. Long-term thyroid replacement was required in several of these individuals. Interferon was stopped in only 3 patients. These findings suggest that therapy with interferon can often be continued despite the onset of treatment-related hypothyroidism.

How Do You Treat the Patient Who Has Failed Conventional Therapy?

Dr. Nazem Afdhal, from Boston Medical Center,[12] also spoke at this clinical symposium on management of hepatitis C. He suggested that patients with HCV genotypes 1 and 4 should be treated for 12 months with combination interferon/ribavirin therapy, and that those with genotypes 2 and 3 be treated with combination therapy for only 6 months. In addition, Dr. Afdhal recommended that those with advanced fibrosis/cirrhosis be considered for 12 months of therapy regardless of HCV genotype, and that patients who failed to achieve a sustained response after only 6 months of therapy may be considered for retreatment with 12 months of therapy. Lastly, he suggested that patients who fail a 12-month combination therapy program should wait for better agents to become available before considering additional therapy; there is currently no role for routine maintenance therapy outside of

clinical trials. Both Dr. Afdhal and Dr. Fried indicated that combination therapy with pegylated interferon and ribavirin might be the best future therapy for patients with HCV infection when this regimen becomes available.

Summary

Chronic infection with HCV is a serious health problem in the United States. Current regimens of combination therapy with interferon-alpha and ribavirin are more effective than interferon monotherapy. However, patients with HCV genotype 1 respond more poorly than those with genotypes 2 and 3 to these regimens. Induction with high-dose interferon prior to initiation of combination therapy does not appear to convey any added advantage to the standard interferon/ribavirin combination regimen.

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Conference Summary - American College of Gastroenterology 65th Annual Scientific Meeting

Post Test

Select an answer for each question. A test score of 70% or greater is required for accreditation.

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1. **The incidence of cancer in a patient with BE is:**
   a. Less than 1% per year
   b. 1% to 5% per year
   c. 5% to 10% per year
   d. More than 10% per year

2. **True or false: Normalization of intraesophageal acid exposure is required to successfully reverse BE with endoscopic techniques.**
   a. True
   b. False

3. **A 24-year-old woman with perianal Crohn's disease has dramatically improved following 3 infusions with infliximab. Two of her 3 fistulas, including a rectovaginal fistula, have closed and a third has stopped draining. Her remission should be maintained with:**
   a. Infliximab every 8 weeks
   b. Metronidazole
   c. 6-mercaptopurine

4. **Despite being prescribed a daily dose of 2.0 mg/kg/day of azathioprine for 6 months, a 32-year-old woman with Crohn's disease continues to experience 8-10 bloody bowel movements per day and abdominal pain before each bowel movement. Her white blood cell count is 5600/mm3. Metabolite levels are checked and show a 6-thioguanine (6-TG) level of 280 pmol/8x108 cells and a 6-methylmercaptopurine (6-MMP) level of 5100 pmol/8x108 cells. Her azathioprine should be:**
   a. Increased to 2.5 mg/kg
   b. Not changed, but she should have 5-aminosalicylic acid added to her regimen

c. Not changed, but she should have allopurinol added to her regimen
d. Discontinued as being ineffective
e. Not changed, but she should be encouraged to be more adherent to medications

5. Which of the following new therapies has been used for ablation of Barrett's esophagus?
a. Argon plasma coagulation
b. Endoscopic mucosal resection
c. Photodynamic therapy
d. All the above

6. As presented in the material on the new developments in endoscopy, new endoscopic methods likely to facilitate the detection of abnormal gastrointestinal mucosa include all of the following EXCEPT:
a. Optical coherence tomography
b. Endoscopic confocal microscopy
c. Flexible endoscopic surgery
d. Spectroscopy and light-scattering analysis

7. Which of the following scenarios is associated with better response to combination interferon-alpha/ribavirin therapy?
a. African American ethnicity
b. Viral titer greater than 2 million copies/mL
c. HCV genotype 2
d. Ethanol consumption

8. True or false: Gender and heredity play a small role in response to drug treatment in IBS patients.
a. True
b. False

9. True or false: The disease burden of IBS is not significantly increased over controls in HMO populations.
a. True
b. False

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Evaluation

Instructions: Please respond to each question to assist activity organizers in evaluating the effectiveness of this activity and plan future activities. Your choice of answers will not affect your credit; however, you must respond to each question in order to receive credit. Please select one answer for each question.

Scale: 5 = Excellent; **4** = Good; **3** = Satisfactory; **2** = Fair; **1** = Poor

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1. Please rate how well you were able to achieve the activity learning objectives:
   a. Summarize the latest trends and topical issues in the fields of gastroenterology and hepatology.
      5 4 3 2 1
   b. Evaluate new diagnostic or therapeutic strategies as they relate to specific clinical entities, including inflammatory bowel disease, irritable bowel syndrome, hepatitis C, and Barrett's esophagus/esophageal adenocarcinoma.
      5 4 3 2 1
   c. Define established and new forms of therapy for diseases of the gastrointestinal tract and liver.
      5 4 3 2 1
   d. Discuss the latest advances in diagnostic and therapeutic endoscopy.
      5 4 3 2 1
   e. Define current concepts in the pathophysiology of diseases of the gastrointestinal tract and liver as they influence the approach to clinical management and affect clinical outcome.
      5 4 3 2 1
   f. Integrate information regarding the diagnosis, prognosis, treatment, and pathophysiology of diseases of the gastrointestinal tract and liver to enhance patient care and improve clinical outcomes.
      5 4 3 2 1

2. Please rate the relevance of activity content to the objectives.
   5 4 3 2 1

3. Please rate the faculty's/author's effectiveness (clarity and organization) in presenting the material.
   5 4 3 2 1

4. Please rate the content and its impact.
   Will definitely change the way you practice
   Challenged you to think about the topics
   Applicable to your practice; a good review
   Of limited use in your practice
   Not applicable to your practice

5. Please rate how well this activity met the goal of summarizing new findings and discussing their practice and research implications.
   5 4 3 2 1

6. Please rate how well your personal objectives for participating in this activity were met.
   5 4 3 2 1

7. If commercial support was offered for this activity, did you feel that the activity was fair, balanced, and free of commercial bias?
   5 4 3 2 1 not applicable

8. How long did this session actually take you to complete?
   .25 - .50 hrs
   .50 - 1.0 hrs
   1.0 - 1.5 hrs
   1.5 - 2.0 hrs
   More than 2.0 hrs

9. What other continuing education topics would be of value to you? Please offer any additional comments.