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After Nearly
40 Years, Is It
Still the Right
Choice Today?

**Hans Herfarth,
MD, PhD,** and
**Russell D. Cohen,
MD, FACC, AGAF,**
share their views.

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Note From the Editor



This issue of *AGA Perspectives* will be the last you receive while I am still the editor. As of the end of the current AGA year, after DDW® 2013, the editorship will no longer be the job of the AGA councillor-at-large. Instead, an individual AGA member independent of the AGA Governing Board will serve as the editor of *AGA Perspectives*. You will learn more about the new editor on the editor's page of the next issue. Since we plan the upcoming issues of *AGA Perspectives* at least six months ahead, it will not be until 2014 that you will see the influence of our new editor in the magazine.

The focus of the April-May 2013 issue is inflammatory bowel disease (IBD), disorders with significant morbidity and mortality that are increasing in prevalence worldwide. Drs. Russell Cohen and Hans Herfarth debate whether the Crohn's Disease Activity Index (CDAI) remains useful in the management of Crohn disease, 40 years after its use in IBD. Dr. Herfarth supports the notion that there is still a role for the CDAI while Dr. Cohen supports the concept that the CDAI should be replaced by other measures, specifically the CDEIS, the Crohn's Disease Endoscopic Index of Severity (CDEIS) which focuses on mucosal healing.

Dr. Claudia Gruss examines the role that capsule endoscopy plays in the monitoring of treatment in established small bowel Crohn's disease. I am pleased to feature my UCSD colleague, Dr. Barrett Levesque, who discusses new developments that have the potential to advance our management of patients with severe ulcerative colitis (UC). We also include a forward thinking perspective on colonic dysplasia surveillance from Dr. Fernando Velayos.

Dr. Judy Cho provides her views on how personalized medicine approaches can enhance IBD management, while Dr. Kim Issacs presents her perspective on whether the risks of biologic therapies are outweighed by their benefits. I believe our readers will also be very interested in the international corner article by Dr. Mamoro Watanabe and his colleagues, that examines IBD in Japan. The graphs showing the marked annual increase in the prevalence of UC and Crohn's speaks to the need to better understand factors that promote development of IBD: food, the microbiome, and other host and environmental factors.

I expect our readers have made plans to attend DDW 2013 and the 2013 AGA Spring Postgraduate Course. As always, attendees can learn the latest updates in clinical care, endoscopic treatments and new research, as well as a venue to see friends and colleagues. It is our first time back to Orlando since DDW 2003. DDW starts on Saturday, May 18, 2013 and finishes at the end of the day on Tuesday May 21, 2013. New for 2013 is a joint AGA and ASGE plenary session on Saturday May 18th morning.

I look forward to seeing everyone at DDW in Orlando and I appreciate your support of *AGA Perspectives* during my time as editor.

Sheila E. Crowe, MD, AGAF
EDITOR

We welcome member feedback on all of the perspectives presented in this issue. Send your letters and comments to communications@gastro.org and include "AGA Perspectives" in the subject line.

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CROHN'S DISEASE ACTIVITY INDEX

After Nearly 40 Years, Is It Still the Right Choice Today?



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*Dr. Herfarth had no relevant
conflicts to disclose.*

Worldwide, at any given time, numerous clinical studies testing novel therapies targeting specific molecules or proteins involved in the inflammatory process of inflammatory bowel diseases (IBD) are actively recruiting Crohn's disease patients. In most of these studies, the Crohn's Disease Activity Index (CDAI) is used as the primary index for evaluation of disease activity at inclusion of the study and to assess therapeutic success of the therapy. The CDAI was developed in the early 1970s when methods that are now considered old-fashioned (e.g. barium enemas) were used to evaluate the GI-tract of Crohn's patients. Essentially, the purpose of the CDAI is to incorporate disease activity indicators in an easy-to-use computational fashion with straightforward data collection in the form of a patient diary. Out of the original 18 presumably disease-related clinical symptoms and factors, eight were derived by regression analysis in a cohort of 118 patients. These eight elements (such as abdominal pain, diarrhea, overall well-being and extra-intestinal manifestations) correlated well with the physician's appraisal of disease activity and were additionally validated using 1,078 patient visits in the National

We have to
reassess the use
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of disease activity
in Crohn's.

Cooperative Crohn's Disease Study and the Trial of Adjunctive Sulfasalazine in Crohn's Disease.¹

However, almost from the onset, shortcomings of this index were apparent with regard to visual evaluation of structural intestinal damage and its correlation with the CDAI. Modigliani impressively demonstrated in 1990, that the CDAI did not correlate with the extent of ileocolonic inflammation.² In fact, patients could be in remission as defined by a CDAI score less than 150 points and still have endoscopically significant colonic inflammation, and vice versa. The findings of Modigliani *et al.*

indicate that the most heavily weighted symptoms of the index — abdominal pain, general well-being and the amount of diarrhea — are not specific features of intestinal inflammation. Thus, patients with irritable bowel syndrome (IBS) can easily achieve CDAI point scores of 450 and higher without evident intestinal inflammation. Only recently have we recognized that an important overlap of IBS and IBD exists and that high numbers of patients with significant abdominal pain and diarrhea might actually not suffer from active inflammation causing these symptoms.³ These patients also very likely do not respond to specific anti-inflammatory therapies, since inflammatory processes do not cause their symptoms. Therefore, if significant numbers of these “non-inflammatory” Crohn's patients are included in clinical trials investigating novel anti-inflammatory therapies using only the CDAI as a criterion for study entry and outcome, these clinical studies might produce negative results even if the potential new drug would work in subpopulations of Crohn's patients with significant intestinal inflammation.

The following trial examples describe the “CDAI dilemma”: the CDAI was originally

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Should Mucosal Healing Be Used Instead?

The Crohn's Disease Activity Index (CDAI) was first introduced as a measure of clinical response and remission (the primary endpoint) in luminal Crohn's disease clinical trials in the 1970's, when the landmark National Cooperative Crohn's Disease Study (NCCDS) was first conducted. Since that time, the CDAI has been used in virtually every major clinical trial involving therapeutic interventions in luminal Crohn's disease, providing an objective "gold-standard" scale¹ which allows unbiased comparison between therapies. The scale was not designed nor used for perianal fistulous Crohn's disease. The need for consistency is more apparent now than ever, as more populations world-wide are reporting increased incidence rates of Crohn's disease, and therapeutic options range from standard pharmaceuticals to biological agents, stem-cell therapies, intentional helminthic infestations and other novel approaches.

The historical relevance of the CDAI cannot be ignored. First described by Best *et al.*² as part of the NCCDS, this index was designed prospectively for patients with Crohn's disease involving the small bowel, colon or both. The equation, generated through multiple logistic regression, contains eight variables that reflect

Table 1: Components and Scoring of the Crohn's Disease Activity Index (CDAI)²

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for seven days.....	x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days.....	x 5
General well-being, assessed from 0 (well) to 4 (terrible) daily for seven days.....	x 7
Presence of complications*	x 20
Taking diphenoxylate/atropine, loperamide, or opiates for diarrhea.....	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite).....	x 10
Hematocrit of less than 0.47 in men and less than 0.42 in women.....	x 6
Percentage deviation from standard weight	x 1
TOTAL SCORE	

*One point each is added for each set of complications:

- Arthralgias or arthritis
- Anal fissures, fistulae or abscesses
- Iritis or uveitis
- Other fistulae
- Erythema nodosum, pyoderma gangrenosum or aphthous ulcers
- Fever during the previous week

the impact Crohn's disease has upon the patient as a whole, rather than just bowel symptoms (Table 1). In order to avoid confounding due to day-to-day variability in many symptoms associated with Crohn's disease, the CDAI is based upon the average of scores of the course of an entire week.

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CDAI SCORE

- Remission: Less than 150
- Response: Decrease greater than 70 points (greater than 100 points in more recent clinical trials.)
- Mild disease: 150 to 220
- Moderate disease: 220 to 450
- Severe disease: Greater than 450



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Dr. Cohen has received lecture fees from Abbott Laboratories, MSD Brail, Salix Pharmaceuticals, Santarus, Schering Plough Mexico, Shire and UCB Pharma. He is a consultant for Abbott Laboratories, Elan Pharmaceuticals, Janssen (Johnson & Johnson/Centocor), Proctor and Gamble Pharmaceuticals, Prometheus Laboratories, Protein Design Labs, Salix Pharmaceuticals, Sanofi-Aventis, Santarus, UCB Pharma and Warner-Chilcott. Dr. Cohen is also the recipient of a research grant from Janssen (Johnson & Johnson/Centocor).

validated in North America and the index may not work as well in Russia and Eastern European countries. A multicenter trial investigating a p38 mitogen-activated protein kinase inhibitor demonstrated significantly higher placebo response and remission rates in these countries according to the CDAI measurements, as compared to countries in Western Europe and North America.⁴ These high placebo rates might be explained by a lower disease activity, a different doctor-patient relationship or just a different disease course compared to the initial validation studies of the CDAI in North America. However, it is also probable that the results reflect the fact that the CDAI is an inferior tool to discriminate between active inflammatory Crohn's from non-inflammatory functional symptoms, which may be caused by factors other than inflammation and intestinal structural damage. Similarly, in the Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) trial, which investigated the efficacy of a novel treatment approach to inhibit leukocyte adhesion and extravasation in the gut using natalizumab, no significant differences between active drug and placebo were found in the induction period after 10 weeks.⁵ Only post-hoc analyses using elevated C-reactive protein (CRP) values at time of inclusion in the study as an additional variable demonstrated a significantly better efficacy of the drug compared to placebo in patients with an elevated CRP, thus excluding patients with normal CRP and most likely no significant intestinal inflammation, but high CDAI values. Without these additional analyses of CRP, the clinical trial would not have revealed a clinical efficacy of this drug and thus this new principle of inhibition of leukocyte adhesion and extravasation might have not been further studied in IBD.

The results of the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial also strikingly illustrates the "CDAI dilemma" in the realm of drug comparative-effectiveness research.⁶ Patients entering the study were required to have active disease defined by a CDAI greater than 220 points. Additionally, at study entry, patients were assessed for active inflammation by CRP and colonoscopy, though these measures did not serve as criteria for inclusion into the trial. The differences between the three therapy arms — azathioprine monotherapy, infliximab monotherapy, and combination therapy of azathioprine and infliximab — regarding proportions of patients in steroid-free remission at week 26 were most pronounced in patients with an elevated CRP and mucosal lesions visualized on colonoscopy (28.0, 56.9 and 78.9 percent, respectively). In contrast, there was no difference in steroid-free remission rates at week 26 between the therapy

arms in patients with no visible mucosal inflammation, but moderate-severe clinical disease activity according to CDAI at study entry (40.7, 33.9 and 40.0 percent respectively). Most likely in this later group, a placebo therapy would have generated the same results, illustrating that a clinical trial using only CDAI as an entry and outcome measure can miss significant therapeutic differences between groups, if a "non-inflammatory Crohn's subgroup" is overrepresented in the study population.

The above examples clearly illustrate that the use of CDAI as the only primary tool of evaluation of disease activity in Crohn's is insufficient. The addition of CRP as a selection marker might serve as a further definition of a subset of patients with moderate to severe inflammation, but it is not a reliable differentiation factor for the groups of Crohn's patients with solely functional problems and no intestinal inflammation and those with mild to moderate disease. Therefore rigorous screening for inflammation using endoscopy and/or other imaging methods, as well as monitoring biomarkers of inflammation such as calprotectin should be required for disease activity evaluation of Crohn's patients entering a therapy study. Regarding evaluation of outcomes, one approach might be the use of composite indices which define remission not only by the CDAI, but also by other measures, such as the absence of both concomitant steroid therapy and surgery during the trial period. Moreover, the addition of endoscopic assessment of mucosal healing (with central reading of the endoscopy procedure) is an exciting and interesting option. The potential clinical trial end point "mucosal healing" needs further validation, especially concerning the potential clinical value to use this marker as a surrogate marker of long-term remission.

There is no doubt that the CDAI has served the IBD clinical trial field well in the past, including facilitating the approval of revolutionary therapies such as anti-TNF agents or budesonide, but it is time for a change. We have to reassess the use of this over 35-year-old tool in the evaluation of disease activity in Crohn's. The aforementioned studies clearly demonstrate that we might miss potentially beneficial therapies for Crohn's patients if we continue to use the CDAI as the only primary outcome instrument. We have to find new ways for evaluation of clinical efficacy, which might be accomplished by combining the CDAI and several other outcome measures in a composite score or by creating a new index with the incorporation of more objective markers of disease activity such as the use of imaging technology to evaluate for structural damage throughout the intestinal tract. ■

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Table 2: Crohn's Disease Endoscopic Index of Severity (CDEIS).⁴

Parameter	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	Total
Deep ulceration (12 if present, 0 if absent)						Total 1
Superficial ulceration (6 if present, 0 if absent)						Total 2
Surface involved by disease (cm)						Total 3
Ulcerated surface (cm)						Total 4

Total 1+2+3+4 = **Total A**

Number of segments totally or partially explored (1-5) = n

TOTAL A/n = **Total B**

Quote 3 if ulcerated stenosis anywhere, 0 if not = **Total C**

Quote 3 if non-ulcerated stenosis anywhere, 0 if not = **Total D**

Total B+C+D = CDEIS

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While this may make it more cumbersome for clinical trial staff to calculate, and limits “on the spot” CDAI calculations in the office, it seems appropriate to avoid hitting that one “bad day” or “good day” and a resulting inaccurate score. The CDAI has been shown to correlate with other validated Crohn’s disease clinical efficacy scales, such as the Harvey Bradshaw Index (HBI), the Cape Town Index and others.

The CDAI has repeatedly been shown to correlate with the most widely studied and accepted measure of health-related quality of life utilized in Crohn’s disease studies, the Inflammatory Bowel Disease Questionnaire (IBDQ).³ This offers further validation that the measures captured by the CDAI are those that matter to the patient, a point that should not be taken lightly given that the patient should be the focus of therapy. Other more generalized health-related quality of life scales have also been shown to correlate with the CDAI as well.

There is not a good correlation, however, between the CDAI and the Crohn’s Disease Endoscopic Index of Severity (CDEIS),⁴ itself a somewhat complicated scale that has not been used in most major clinical trials (Table 2). This “disconnect,” as well as the failure of the CDAI to correlate well with mucosal healing in more recent Crohn’s disease trials suggests that mucosal appearance may not be an appropriate measure of Crohn’s disease activity. Unlike ulcerative colitis, which is purely a mucosal disease, the transmural nature of Crohn’s disease, as well as involvement of the small intestine (virtually unexplored by routine endoscopy) argues against depending solely upon the mucosal appearance when determining the presence and severity of disease activity. More recently, a video capsule endoscopy (VCE) Crohn’s disease activity index (CECDAI) has been proposed,⁵ based upon small bowel findings on VCE; this too failed to correlate with either the CDAI or the IBDQ, giving further credence to the principle that mucosal appearance alone is not an adequate assessment of Crohn’s disease activity.

Supporting this contention that endoscopic criteria (i.e. mucosal healing) is not an appropriate surrogate marker for Crohn’s disease activity in this transmural disease has been the findings that transmural radiographic evaluations have shown correlation with the CDAI. Recent studies of the use of MRI to evaluate the disease activity in patients with small bowel Crohn’s has shown a good correlation between MRE findings suggestive of active Crohn’s and the CDAI, as well as the IBDQ. Studies with CT-enterography have also shown correlation with CDAI as well as biomarkers of active disease. Contrast-enhanced ultrasound has failed to correlate with CDAI; however, it also has not correlated well to other biomarkers of inflammation.

Since its inception, weaknesses of the CDAI have been postulated, and in some instances, interventions or adjustments have been made. Intra-observer and inter-observer variability in scoring the CDAI has been shown to decrease with adequate training of the staff responsible for the scoring. Patient confusion resulting in ambiguous reporting has likewise been tempered with more clear objective instructions from better-trained study staff. Concern over the use of only a 70-point decline to indicate a clinical response has resulted in the adoption of a 100-point decline as the clinical response endpoint in most of the more recent clinical trials.

The CDAI remains the gold standard in measuring disease activity for patients with luminal Crohn’s disease. It correlates well with other accepted disease activity scales, as well as the gold-standard measurement of health-related quality of life, the IBDQ. The failure of the CDAI to correlate with newer indices focused on mucosal appearance by colonoscopy (CDEIS) or video capsule endoscopy (CECDAI) suggests that a transmural disease needs a transmural evaluation of activity, as shown by MRE and CTE. Thus, while “mucosal healing” may be adopted as a primary endpoint in ulcerative colitis, it does not seem to be appropriate in Crohn’s disease. There certainly are weaknesses with the CDAI; however, to date there have been no stronger comprehensive evaluations of Crohn’s disease activity to replace its use in clinical trials. ■

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Assessing the Utility of Small Bowel Capsule Endoscopy to Monitor Therapy in Known Crohn's Disease



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Small bowel capsule endoscopy (CE) has revolutionized small bowel imaging since its introduction in 2001. We now have a tool to visualize the entire small bowel mucosa just by swallowing a capsule the size of a big vitamin pill. The use of this technology for the diagnosis of obscure gastrointestinal bleeding is well established, but its role in the evaluation of Crohn's disease, especially in patients with known Crohn's, has remained controversial. In this commentary, I will address situations where I feel that CE can be useful in monitoring therapy of patients with known Crohn's disease, as well as highlight areas of concern.

A common clinical situation is the patient with Crohn's who has unexplained gastrointestinal bleeding or iron-deficiency anemia, despite evaluation. CE has been shown to be the most sensitive test for finding small bowel lesions in these patients, with a high diagnostic yield.

CE can be valuable in post-operative surveillance for recurrent disease activity in Crohn's patients after bowel resection. If the anastomotic site cannot be reached with a standard colonoscope, CE is preferable to double balloon enteroscopy in terms of potential risks, costs and availability. Also, CE often finds more proximal lesions. However, these lesions are often minor and are of uncertain clinical significance.

A challenging conundrum is when a Crohn's patient has gastrointestinal symptoms not responding to standard therapy, especially when faced with potential pharmacologic choices that may have increased side effects or complication risks. It is not uncommon for Crohn's patients to have other concomitant diseases contributing to symptoms, including irritable bowel syndrome. CE is ideally suited to evaluate a patient's small bowel disease activity, as well as find potential other etiologies of the patient's symptoms, which may influence changes in the patient's management. A CT or MR enterography may underestimate the patient's disease activity, especially in the proximal small bowel, although these radiographic tests are better than CE at evaluating the patient for transmural damage, or extra-intestinal disease or complications.

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Capsule endoscopy is ideally suited to assess the extent and severity of small bowel disease and response to therapy.

Newer classes of drugs, including biologics and other immunomodulators, have changed our goals for treating Crohn's. Symptomatic remission has been shown not to correlate well with mucosal healing. Our new therapeutic endpoint is treating to endoscopic remission. The goal is to avoid future development of fistulizing and stricturing disease. There is evidence that patients who do respond to therapy with endoscopic healing have better outcomes than patients who do not meet this goal. CE is ideally suited to assess the extent and severity of small bowel disease and response to therapy.

So why aren't more CE studies done for the evaluation of patients with known Crohn's? There is the risk of small bowel capsule retention, which has been reported to be as high as 13 percent in patients with known Crohn's. Radiological studies are unable to rule out this possibility. A patency pill can be administered to an at-risk patient prior to the exam to assess the risk of capsule retention, although timely passage of the patency capsule is not 100 percent sensitive. In a recent retrospective study,¹ the negative predictive value of both tests was not significantly different. I would recommend a patency pill evaluation in patients who have any symptoms suggesting obstruction despite a negative radiological exam. Fortunately, a retained capsule often passes spontaneously or after treatment of active disease. The capsule can often be removed by double balloon enteroscopy. Surgery is indicated rarely, usually when there is a fixed stricture. I recommend that physicians discuss the risk of capsule retention with their patients prior to proceeding with a CE and have a plan in place for what to do if this eventuality occurs.

I feel that we need better prospective evidence to show that aggressive treatment of Crohn's disease to endoscopic healing will positively affect the natural history of the disease. If this standard is validated, then CE may become an important tool in our armamentarium. However, we will need more studies to assess what will become the ideal combination of tests to confirm this goal, which may also include a combination of fecal biomarkers, endoscopy and radiological studies.

In my opinion, ileo-colonoscopy, CTE and MRE usually will provide the information that we need to guide our therapy in patients with known Crohn's. However, in cases where management decisions are not clear despite the use of these modalities, CE can be an invaluable tool and worth the potential risk of capsule retention. I would have a low threshold, however, for performing a patency capsule test prior to initiating a CE study. ■

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Advancing the Management of Severe Ulcerative Colitis



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A severe flare of ulcerative colitis (UC) remains a clinical challenge. Severely ill, hospitalized patients face important risks of toxic megacolon and fulminant disease. Despite their significant side effects and lack of long-term efficacy, corticosteroids have remained the mainstay of acute therapy since the landmark studies of Truelove and Witt. Cyclosporine is an effective salvage second-line therapy, but its widespread use is limited by safety concerns and, similar to corticosteroids, lack of long-term efficacy. Infliximab has emerged as an alternative therapy for severe UC, yet until recently, clinicians have lacked robust randomized trials supporting its efficacy in this setting. Finally, with these narrow opportunities for medical therapy success, eventual colectomy is avoided in only 40 to 50 percent of patients.

There are a number of fundamental tactics that can be utilized to optimize patient outcomes. Initial steps include ruling out confounding conditions that may mimic or exacerbate UC: checking for *Clostridium difficile* and other bacterial infections, stopping aminosalicylates, and performing a sigmoidoscopy to assess severity and exclude cytomegalovirus infection. Toxic megacolon should be excluded with an abdominal radiograph. Thromboembolism prophylaxis should be initiated, and heparin is not contra-indicated. There is no evidence that bowel rest or total parenteral nutrition improves outcomes in severe UC. Patients are treated with intravenous steroids, at a dose equivalent to 1mg/kg body weight daily of methylprednisolone, which is successful in inducing a response about half of the time. There is little evidence to support higher doses or alternative dosing corticosteroid regimens. A consultation with the colorectal surgery team enables patients to discuss surgical options and prepare for surgery if second-line therapy fails. After 72 hours, ongoing bloody diarrhea and a high C-reactive protein are indicators for second-line therapy with infliximab. Cyclosporine can also be considered in thiopurine-naïve patients. By day five, infliximab or intravenous cyclosporine should be initiated, and if patients do not respond within five to seven days, then surgery is recommended. Salvage therapy with sequential infliximab and cyclosporine carries high risk of infection and should generally be avoided. In severe UC, a three-stage procedure is preferred by many colorectal surgeons if an ileal pouch-anal anastomosis is planned.

Advancing the care of severe UC beyond this paradigm involves educating clinicians, implementing effective guidelines, researching how to best utilize and choose between existing therapies, and conducting clinical trials of novel therapies. A better outcome measure for clinical trials in patients with severe UC disease activity is also needed. A recent AGA Institute

There are several recent incremental advances to consider in your practice.

publication on the treatment of hospitalized severe UC includes algorithms for the management of severe UC that can be incorporated into electronic medical record systems.¹ Clinicians now have additional data to inform their choice between infliximab and cyclosporine. A recent study by Laharie and colleagues evaluating their comparative effectiveness did not find a significant difference in treatment failure by 98 days of therapy (54 and 60 percent, respectively).² It is important to note that the dose of cyclosporine has been maximized in the trial and is limited by side effects. Conversely, patients with severe UC have been shown to have high clearance of the infliximab, and may require higher dosing in order to maintain a therapeutic trough which is associated with greater likelihood of response, remission and mucosal healing.³ The addition of an immunomodulator may help reduce antibody formation, and maintain trough levels. In contrast to cyclosporine, there does not appear to be dose-limiting toxicity with anti-tumor necrosis factor alpha therapy.

There are several recent incremental advances to consider in your practice. Consider identifying eligible patients early on in their admission (day two through four) that are failing other outpatient therapy, and initiate infliximab as a potentially efficacious induction and maintenance therapy. Patients who are being treated with outpatient infliximab and present with a severe flare now have assays available to assess for rapid clearance resulting in under-dosing, presence of anti-drug antibodies to infliximab or lack of response to anti-tumor necrosis factor alpha therapy despite adequate drug concentrations. Patients with anti-infliximab antibodies may be candidates for adalimumab, although the optimal dosing schedule in severe UC remains to be determined. Patients who initially respond to infliximab 5mg/kg body weight, but then lose response between doses, may have high clearance and benefit from an earlier and/or 10mg/kg next dose.

In the future, real-time therapeutic biologic drug concentration monitoring and care pathway trials will help optimize these regimens, and continue to advance our management of severe UC. ■

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Colonic Dysplasia Surveillance in IBD: 2013 and Beyond



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Dr. Velayos had no relevant conflicts to disclose.

Gastroenterologists routinely perform colonoscopy for screening/surveillance with the goal of preventing colorectal cancer. Notable is that the same procedure (colonoscopy) for the same indication (screening/surveillance) in inflammatory bowel disease (IBD) patients often creates stress and even confusion. Colonic dysplasia surveillance in IBD has its own guidelines, vocabulary and technique. There are numerous reports of cancer occurring despite close monitoring. We fortunately continue to refine our approaches. There are a few key facts and principles to remember when performing colonic dysplasia surveillance in IBD for 2013 and beyond.

Surveillance guidelines differ, but are consistent regarding timing of first exam and that follow-up exams should be more frequent than in non-IBD patients.

Published guidelines for surveillance in IBD agree that the first screening colonoscopy should be performed in all patients eight to 10 years after diagnosis and immediately in patients with primary sclerosing cholangitis to determine extent. In deciding extent, I use histologic evidence of colitis rather than only endoscopic evidence. Surveillance should be performed when disease is relatively quiescent and stable.

With regard to when to perform the next colonoscopy, guidelines differ. I recommend subsequent colonoscopies every one to two years for surveillance, consistent with a majority of the US-based societal guidelines. Typically only the affected segment in the case of left-sided ulcerative colitis needs surveillance. I do not routinely perform surveillance in the affected rectum of proctitis patients unless the disease is moderate to severe. I do not routinely perform colonic surveillance in patients with Crohn's isolated exclusively to the ileum as these patients do not harbor an increased risk of cancer in the colon due to an inflamed small bowel.

Deciding the interval between exams is an imprecise science.

Unfortunately, there is no guidance regarding who should get a colonoscopy every year versus every two or even three years. Often I will use the presence of colorectal cancer risk factors, such as moderate inflammation, strong family history of colorectal cancer, pseudopolyposis and the presence of primary sclerosing cholangitis to identify patients who should undergo yearly surveillance. The most recent British Society of Gastroenterology guidelines are quite novel in that, for the first time, colorectal cancer risk factors were used to define higher, medium and lower risk groups which translate into yearly, three-year and five-year surveillance recommendations, respectively. This approach has not been incorporated yet into US-based guidelines.

Most dysplasia is visible and each minute of withdrawal increases dysplasia detection.

Nearly 75 percent of dysplastic lesions in IBD are visible on colonoscopy and each minute of withdrawal time has been shown to increase the detection of dysplasia in IBD surveillance. Yet it often seems that most of the time during surveillance is occupied with performing random biopsies to detect "flat" dysplasia. It is also important to remember to detect the "non-flat" dysplasia. These visible dysplastic lesions may be subtle and without careful examination may blend more readily to the background of inflamed mucosa or inflammatory polyps. Regardless, these data are useful reminders that simply performing 33 random biopsies should not be the only goal, or substitute as effective surveillance in IBD patients. It is important to sample and biopsy any areas that may be slightly more erythematous or nodular or that look distinct in any way from the underlying inflamed mucosa.

It is OK to simplify dysplasia vocabulary.

Although I still will use the terms "adenoma-like lesion or mass", "dysplasia associated lesion or mass", as well as "flat dysplasia", I agree with the effort to simplify and create a less ambiguous vocabulary. I find it much more helpful to define dysplasia based on how it was detected, specifically whether it was detected on non-targeted biopsies (random biopsies) or on targeted biopsies. Clearly, success of such nomenclature depends on the random biopsies being truly random. Thus, for me, a patient with dysplasia detected on non-targeted biopsies truly has "flat" or "invisible" dysplasia. In contrast, someone with dysplasia detected on targeted biopsies, even if it does not look like a traditional polyp, could in theory have its borders defined and thus a judgment can be made as to whether it can be resected endoscopically or not.

Chromoendoscopy increases dysplasia detection rate; "virtual" chromoendoscopy does not.

Use of methylene blue or indigo carmine dye spray (chromoendoscopy) during IBD surveillance to: 1) highlight subtle mucosal abnormalities so that 'invisible' lesions become more visible; and 2) accentuate the pit pattern of the mucosa to distinguish between neoplastic and non-neoplastic lesions, has been shown in several high-quality studies to increase dysplasia detection rate. On the other hand, use of post-processing techniques or rotating filters to create a pseudocolored picture that mimics dye spray chromoendoscopy (virtual chromoendoscopy) has not demonstrated a consistent benefit. Current AGA guidelines suggest dye spray chromoendoscopy is an acceptable alternative to random biopsies for gastroenterologists with expertise in this technique. They do not yet advocate it as the standard of care for all examinations. ■

Prospects for Individualized Medical Management in IBD



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Advances in high-throughput sequencing, “-omic technologies” (microbiome, metabolome) and potential data from electronic medical records all point to the possibilities for personalizing medical management through the acquisition and interpretation of large amounts of new data. Recent advances in the identification of genetic loci associated with inflammatory bowel disease (IBD) have provided important insight into the broad range of disease-associated genes in IBD. In this perspective, we will discuss the possibilities for genetic analyses — most likely in concert with other, large datasets — for providing important assistance in individualizing medical management for patients with IBD.

Genetic architecture of IBD

In a large-scale, international effort, 163 genetic loci were significantly associated with IBD.¹ These loci implicate a broad range of likely disease genes, including cytokines, cytokine receptors, trafficking molecules and genes mediating host recognition of microbial products. Importantly, 110 of these 163 loci confer risk to IBD generally, with 30 and 23 loci conferring risk specifically to Crohn’s disease and ulcerative colitis, respectively. Enrichment analyses of these genetic associations implicate a variety of different immune cell types in driving disease, and many genes play a key role in mediating host responses to a variety of infectious agents. Importantly, many of these loci demonstrate overlap with other immune-mediated diseases; patterns of association that may provide important clues in prioritizing therapeutic agents in different diseases.

Prominent among these patterns are the shared associations between IBD and psoriasis in multiple genes involving the pro-inflammatory interleukin 12/23 (IL-12/23) pathways. An uncommon protective allele present in approximately one out of every seven healthy individuals of European ancestry at codon 381 in the IL-23 receptor gene,² confers a three-fold protection against developing IBD. Importantly, this uncommon protective allele is a relative loss-of-function allele,^{3,4} and therefore suggests that decreasing IL-23 signaling may be effective in treating these diseases. A monoclonal antibody against the p40 subunit (cytokine subunit common to IL-12 and IL23 cytokines) has been approved for the treatment of psoriasis,⁵ with evaluation in IBD ongoing.

Genes and therapies

Relatively uncommon, loss-of-function alleles that decrease disease risk highlight potentially ideal therapeutic targets. The presence of naturally occurring, loss-of-function alleles in healthy individuals would suggest that blocking that particular pathway might be

both safe and effective in treatment at the earliest possible stages of disease pathogenesis. For example, loss-of-function alleles in proprotein convertase subtilisin/kexin type 9 (PCSK9) are associated with decreased levels of LDL cholesterol⁶ and development of agents to block PCSK9 are actively ongoing.

In addition to highlighting potential new therapeutic targets, evaluation of genetic variation may play an increasingly important role in assessing the safety and efficacy of various therapeutic agents for individual patients. Because medical therapies are a relatively recent human development — and thus not selected for evolutionarily — large inter-individual differences in responses to therapeutic agents commonly exist. Inter-individual variation in activity of the drug-metabolizing enzyme, thiopurine methyltransferase (TPMT), is routinely evaluated prior to institution of 6-mercaptopurine. As new IBD therapies are introduced, it is likely that pharmaco-genetics will play an important role in screening individuals more likely to have adverse reactions to specific agents.

Need for integration of different data-types

Less clear at this point is whether genetics alone will provide a means of individualizing medical management based on efficacy of various therapeutic agents. The need for tailoring therapies for individual patients with IBD may become increasingly relevant in the near future as new classes of therapies become available. Given the patho-physiologic complexity inherent in IBD, it is unlikely that genetics alone will provide sufficient information for most effectively tailoring medical management. The clinical picture of a patient with IBD results from a complex interaction of genetic, environmental, developmental and disease course factors, such as the patient’s age, nutritional status and presence of co-morbidities. There is an urgent need for the development of improved biomarkers in IBD, both to classify patients more effectively, as well as to more precisely follow disease course. While the large majority of loci are associated to IBD generally, it should be noted that the largest effect loci, such as the nucleotide oligomerization domain 2 and major histocompatibility complex class II associations, are specific to Crohn’s disease or ulcerative colitis, respectively.¹ This suggests the presence of significant patho-physiologic heterogeneity in IBD, especially with respect to differences in host interactions with the intestinal microbiome. Given the rapid progress in this field, it may be anticipated that intestinal microbiome analyses, integrated with genetics and improved immunologic analyses, may provide an important means of individualizing medical therapies in patients affected by IBD. ■

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DEXILANT WORKS A SECOND SHIFT TO HELP SHUT DOWN ACID PUMPS

Conclusions of comparative efficacy cannot be drawn from this information.

96% OF 24-HOUR PERIODS REMAINED HEARTBURN FREE IN A 6-MONTH STUDY¹

Overall treatment Median percentage of 24-hour heartburn-free periods of the maintenance of healed EE study vs 29% with placebo. Secondary efficacy endpoint, $p < 0.0025$.^{1,2}

DEXILANT 30 mg (n=132); Placebo (n=141)

DEXILANT 30 mg provides effective maintenance of EE healing

- 66% of patients remained healed over 6 months with DEXILANT 30 mg (n=125) vs 14% with placebo (n=119; $p < 0.00001$). Study primary endpoint.^{1,2}

Results of a 6-month, multicenter, double-blind, placebo-controlled, randomized study of patients who had successfully completed an EE study and showed endoscopically confirmed healed EE. Based on crude-rate estimates, patients who did not have endoscopically documented relapse and prematurely discontinued were considered to have relapsed.

Indications for DEXILANT (dexlansoprazole)

- Healing all grades of erosive esophagitis (EE) for up to 8 weeks
- Maintaining healing of EE and relief of heartburn for up to 6 months
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks

Important Safety Information

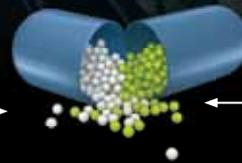
- DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use.
- Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea.
- Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.
 - Most commonly reported adverse reactions were diarrhea (4.8%), abdominal pain (4.0%), nausea (2.9%), upper respiratory tract infection (1.9%), vomiting (1.6%), and flatulence (1.6%).
 - Do not co-administer atazanavir with DEXILANT because atazanavir systemic concentrations may be substantially decreased. DEXILANT may interfere with absorption of drugs for which gastric pH is important for bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole). Patients taking concomitant warfarin may require monitoring for increases in international normalized ratio (INR) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Concomitant tacrolimus use may increase tacrolimus whole blood concentrations. DEXILANT may increase serum levels of methotrexate.
- Please see adjacent brief summary of prescribing information for DEXILANT.

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DDR DEXILANT WORKS WITH A DUAL DELAYED RELEASE FORMULATION

Granule 1 begins releasing drug within an hour of dosing



Granule 2 provides a second release of drug with another peak concentration several hours after dosing

Artistic rendition of granules.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

DEXILANT (dexlansoprazole) delayed-release capsules for oral use

INDICATIONS AND USAGE

DEXILANT is indicated for:

- healing of all grades of erosive esophagitis (EE) for up to 8 weeks
- maintaining healing of EE and relief of heartburn for up to 6 months
- the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks

CONTRAINDICATIONS

DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use [see *Adverse Reactions*].

WARNINGS AND PRECAUTIONS

Gastric Malignancy

Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.

Clostridium Difficile Associated Diarrhea

Published observational studies suggest that PPI therapy like DEXILANT may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see *Adverse Reactions*].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see *Adverse Reactions*].

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see *Adverse Reactions*].

Concomitant use of DEXILANT with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients [see *Drug Interactions*].

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

Most Commonly Reported Adverse Reactions

The most common adverse reactions ($\geq 2\%$) that occurred at a higher incidence for DEXILANT than placebo in the controlled studies are presented in Table 2.

Table 2: Incidence of Adverse Reactions in Controlled Studies

Adverse Reaction	Placebo (N=896) %	DEXILANT 30 mg (N=455) %	DEXILANT 60 mg (N=2218) %	DEXILANT Total (N=2621) %	Lansoprazole 30 mg (N=1363) %
Diarrhea	2.9	5.1	4.7	4.8	3.2
Abdominal Pain	3.5	3.5	4.0	4.0	2.6
Nausea	2.6	3.3	2.8	2.9	1.8
Upper Respiratory Tract Infection	0.8	2.9	1.7	1.9	0.8
Vomiting	0.8	2.2	1.4	1.6	1.1
Flatulence	0.6	2.6	1.4	1.6	1.2

Adverse Reactions Resulting in Discontinuation

In controlled clinical studies, the most common adverse reaction leading to discontinuation from DEXILANT therapy was diarrhea (0.7%).

Other Adverse Reactions

Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system:

Blood and Lymphatic System Disorders: anemia, lymphadenopathy

Cardiac Disorders: angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia

Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo

Endocrine Disorders: goiter

Eye Disorders: eye irritation, eye swelling

Gastrointestinal Disorders: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hemochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage, retching

General Disorders and Administration Site Conditions: adverse drug reaction, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, nodule, pain, pyrexia

Hepatobiliary Disorders: biliary colic, cholelithiasis, hepatomegaly

Immune System Disorders: hypersensitivity

Infections and Infestations: candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection, vulvo-vaginal infection

Injury, Poisoning and Procedural Complications: falls, fractures, joint sprains, overdose, procedural pain, sunburn

Laboratory Investigations: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase

Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia

Nervous System Disorders: altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia

Psychiatric Disorders: abnormal dreams, anxiety, depression, insomnia, libido changes

Renal and Urinary Disorders: dysuria, micturition urgency

Reproductive System and Breast Disorders: dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchitis, cough, dyspnoea, hiccups, hyperventilation, respiratory tract congestion, sore throat

Skin and Subcutaneous Tissue Disorders: acne, dermatitis, erythema, pruritis, rash, skin lesion, urticaria

Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to DEXILANT by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, cholecystitis acute, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tonsillitis.

Other adverse reactions not observed with DEXILANT, but occurring with the racemate lansoprazole can be found in the lansoprazole prescribing information, ADVERSE REACTIONS section.

Postmarketing Experience

The following adverse reactions have been identified during post-approval of DEXILANT. As these reactions are reported voluntarily from a population of

uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura

Ear and Labyrinth Disorders: deafness

Eye Disorders: blurred vision

Gastrointestinal Disorders: oral edema, pancreatitis

General Disorders and Administration Site Conditions: facial edema

Hepatobiliary Disorders: drug-induced hepatitis

Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)

Infections and Infestations: *Clostridium difficile* associated diarrhea

Metabolism and Nutrition Disorders: hypomagnesemia, hyponatremia

Musculoskeletal System Disorders: bone fracture

Nervous System Disorders: cerebrovascular accident, transient ischemic attack

Renal and Urinary Disorders: acute renal failure

Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness

Skin and Subcutaneous Tissue Disorders: generalized rash, leukocytoclastic vasculitis

DRUG INTERACTIONS

Drugs with pH-Dependent Absorption Pharmacokinetics

DEXILANT causes inhibition of gastric acid secretion. DEXILANT is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, DEXILANT should not be co-administered with atazanavir.

DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

Warfarin

Co-administration of DEXILANT 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with DEXILANT and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Tacrolimus

Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Clopidogrel

Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects

Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, DEXILANT should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60 mg per day) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human lansoprazole dose and in pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human lansoprazole dose revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the

administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies [see *Nonclinical Toxicology*], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of DEXILANT in pediatric patients (less than 18 years of age) have not been established.

Geriatric Use

In clinical studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dosage adjustment of DEXILANT is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole.

Hepatic Impairment

No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

OVERDOSAGE

There have been no reports of significant overdose of DEXILANT. Multiple doses of DEXILANT 120 mg and a single dose of DEXILANT 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT 60 mg include hot flashes, contusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Serum Gastrin Effects

The effect of DEXILANT on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT 30 mg and 60 mg doses. In patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with DEXILANT 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats [see *Nonclinical Toxicology*].

Effect on Cardiac Repolarization

A study was conducted to assess the potential of DEXILANT to prolong the QT/QT_c interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QT_c intervals compared to placebo.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m²) basis of a 50 kg person of average height [1.46 m² body surface area (BSA)] given the recommended human dose of lansoprazole 30 mg per day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats [see *Clinical Pharmacology*].

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day

(4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended human lansoprazole dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the *in vitro* human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

To ensure the safe and effective use of DEXILANT, this information and instructions provided in the FDA-approved Medication Guide should be discussed with the patient.

Inform the patient to watch for signs of an allergic reaction as these could be serious and may require that DEXILANT be discontinued.

Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [see *Warnings and Precautions*].

Advise the patient to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [see *Warnings and Precautions*].

Advise the patient to tell their health care provider if they take atazanavir, tacrolimus, warfarin and drugs that are affected by gastric pH changes [see *Drug Interactions*].

Advise the patient to follow the dosing instructions in the Medication Guide and inform the patient that:

- DEXILANT is available as a delayed-release capsule.
- DEXILANT may be taken without regard to food.
- DEXILANT should be swallowed whole.
- Alternatively, DEXILANT capsules can be administered as follows:
 - Open capsule;
 - Sprinkle intact granules on one tablespoon of applesauce;
 - Swallow immediately. Granules should not be chewed.
 - Do not store for later use.

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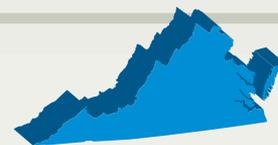
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Do the Benefits of Biologics Outweigh the Risks in Crohn's?



Kim L. Isaacs,
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Professor of Medicine,
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Dr. Isaacs is a member of Janssen's data safety monitoring board, is a member of the ACG Practice Parameters Committee and receives clinical trial support from Given, Elan, UCB, Janssen Millennium, Glaxo and Abbott.

The pre-biologic era

In the 1970s and 80s we had very few options for the primary therapy of Crohn's disease. Oral corticosteroids and sulfasalazine were the mainstays of therapy. We very often found ourselves treating complications of disease including obstruction and abscess formation. Surgical therapy for management of complications was common. In the 1980's, it was not uncommon to have several patients on the gastroenterology in-patient service that were on their fourth or fifth intestinal resection for Crohn's disease. Short bowel syndrome secondary to extensive small bowel resection was seen frequently. At 15 years of disease over 70 percent of patients with Crohn's had at least one surgery.¹ (Table 1)

Significant steroid side effects such as avascular necrosis, compression fractures of the vertebrae, weight gain, mood swings and depression were commonly seen. During this time period, physicians often recommended that women avoid pregnancy due to concerns of disease management and the effects of disease activity and drugs on the fetus. In the pediatric population, growth retardation due to steroids was the norm rather than the exception.

Benefits of the intervention

Increasing use of immunomodulators, such as thiopurines, and the introduction of infliximab in 1998 has changed the course of disease in many patients. Anti-tumor necrosis factor alpha (anti-TNF) therapy has had a dramatic effect on initial clinical response (60 to 70 percent) and clinical remission in patients with Crohn's.² It appears to be most efficacious in patients who have had a shorter duration of disease. Clinically, we see these drugs working very quickly — similar to the speed of response of corticosteroids. Most of our long-term data in the use of anti-TNF agents is with infliximab (1998); however, adalimumab (2007) and certolizumab (2008) appear to have many similar characteristics that are reflective of the drug class.

This class of drugs also leads to mucosal healing in many patients. Pilot studies looking at anti-TNF therapy for prevention of post-operative recurrence in Crohn's have been encouraging. Studies have demonstrated a decreased surgery rate in patients on anti-TNF therapy as well as decreased hospitalizations within the first one to two years of therapy.² With these interventions we are seeing fewer patients with Crohn's disease on their fourth or fifth resection for refractory disease.

With the addition of biologics as well as immunomodulators we have more directed therapy and are able to manage many more patients in the outpatient setting. Patients are often able to avoid steroid therapy for induction of remission. Additionally, the biologic medications that we have available are

Table 1: Crohn's Disease and Surgery in the Pre-Biologic Era¹

Years After Diagnosis	Number of Surgeries			
	1	2	>3	0
5	37%	7%	5%	51%
10	39%	11%	12%	29%
15	34%	14%	22%	30%

Increasing use of immunomodulators, such as thiopurines, and the introduction of infliximab in 1998 has changed the course of disease in many patients.

all large proteins and do not cross the placenta in the first trimester of pregnancy, increasing the comfort level of young women who desire to conceive. Data on pregnancy outcomes while on anti-TNF medications have been reassuring thus far.

Natalizumab (2008) is the first biologic approved for Crohn's disease that has a different mechanism of action — inhibition of lymphocyte trafficking to the gut and brain by targeting $\alpha 4$ integrin. This drug is approved for patients who have failed conventional therapy and at least one anti-TNF.²

Risk of biologics

What then are the concerns?

In terms of disease management, loss of continued response to therapy is important. It is estimated that there is about a 13 percent loss of response per patient year with the use of anti-TNF agents.³

There also have long been concerns that with immune system manipulation that we may be causing patients to have will create new sets of issues — malignancy and infections have been the major worries.

Now that we are 15 years out, what do we know about the risks?

In our practice, we have certainly seen complications of anti-TNF therapy, but most have been very manageable. Lymphoma risk is in the range of a two- to five-fold increase, but still remains fairly uncommon (less than 1:1000). Tuberculosis risk is known with anti-TNF

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therapy, but is minimized by appropriate ongoing screening.

With anti-TNF therapy clinically, we have seen increased viral issues with human papilloma virus infection (warts) and varicella zoster (shingles). Immunologic issues such as psoriasis, arthritis and drug-induced systemic lupus erythematosus have been seen in an increasing number of patients, though these effects tend to resolve when the drug is discontinued. In the Crohn's Therapy Resource, Evaluation and Assessment Tool (TREAT) registry there were more infections in patients treated with infliximab, however disease severity, treatment with prednisone and narcotic use were associated with higher risks of infection and mortality.⁴

Side effects unique to certain classes of drug have emerged as well. Natalizumab has

been associated with progressive multifocal leukoencephalopathy in patients who have previously been exposed to the JC polyoma virus. The development of an antibody test for the JC virus has allowed for risk stratification of patients contemplating the use of natalizumab.⁵

Conclusions

As we move forward into the next two to three decades of IBD therapy, we will face a series of challenges. We must:

1. Identify disease targets and patients who will benefit the most by certain classes of drugs.
2. Design treatment strategies that will decrease loss of response to therapy.
3. Identify individual risk factors for aggressive

disease and treat those patients accordingly to change the natural history of disease.

4. Develop strategies that will minimize neoplastic and infectious risks of our targeted drug therapies.

Yes, biologics are important steps forward in the management of IBD — and we need to continue to re-evaluate and optimize how we use these drugs to make sure there are continued long-term benefits. Anti-TNF and natalizumab therapies are only the beginning of our use of biologics in Crohn's disease. On the horizon are multiple "new" biologics directed at targets such as $\alpha 4\beta 7$ Integrin on lymphocytes (vedolizumab) and the p40 subunit of interleukin-12 and interleukin-23 (ustekinumab). We are entering a very complex but exciting era of Crohn's disease management. ■

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By Pieter Vermeersch, *et al.*

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By Elliot Lee, *et al.*

Waist-to-Hip Ratio, but Not Body Mass Index, is Associated With an Increased Risk of Barrett's Esophagus in White Men

By Jennifer R. Kramer, *et al.*

Gastrointestinal Complications of Cystic Fibrosis

By Daniel Gelfond, *et al.*

Proton Pump Inhibitors Reduce the Risk of Neoplastic Progression in Patients With Barrett's Esophagus

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GASTRO FOR APRIL

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CGH FOR MAY

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By Wenjing Wu, *et al.*

Foxf2 in Intestinal Fibroblasts Reduces Numbers of Lgr5+ Stem Cells and Adenoma Formation by Inhibiting Wnt Signaling

By Ali Moussavi Nik, *et al.*

Perspectives for IBD in Japan

A nation-wide effort to improve management of inflammatory bowel disease



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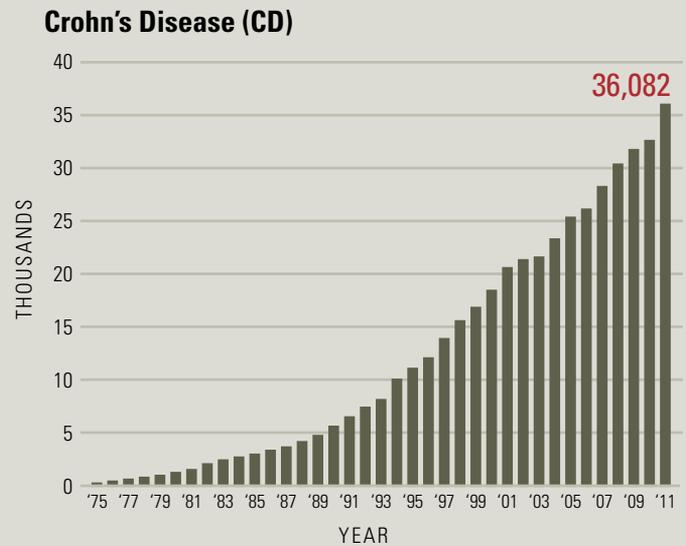
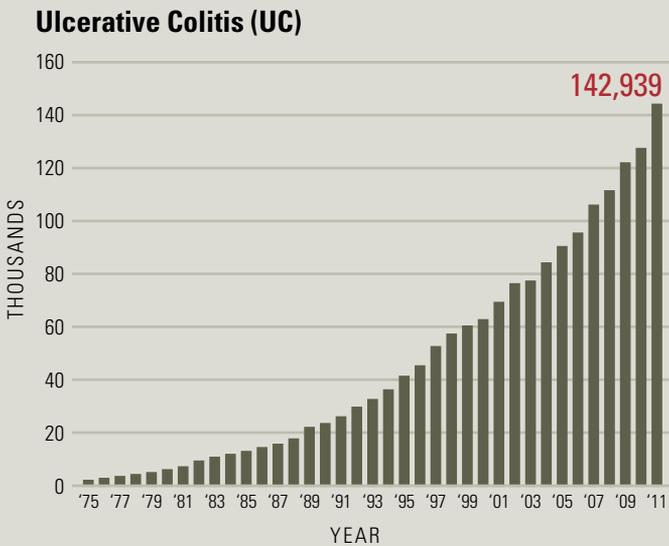
Since the 1970's, patients of ulcerative colitis (UC) and Crohn's disease in Japan have been continuously surveyed, which has clearly shown that the number of both UC and Crohn's patients has dramatically increased during the past decades (see figure). Therefore, IBD has become a common disease that even general gastroenterologists have to know how to manage. In addition to its high prevalence, "ulcerative colitis" has become familiar among people in general since our new prime minister has confessed that he is one of the 140,000 UC patients in Japan.

Government-aided system supports IBD patients, clinicians and researchers.

In Japan, UC and Crohn's have been designated as one of the "intractable diseases (Nanbyo)", and therefore support by the government is provided through the Specific Disease Treatment Research Program (SDTRP). Upon diagnosis of IBD, patients are encouraged to apply for this national program by providing their clinical data to the local health center. Once their application has been accepted, the program shoulders most part of the patient's medical

IBD has become a common disease in Japan.

Year-by-Year Increase of IBD patients in Japan



expense, limiting their own expenses from 0 to 23,100 yen per month (~0 to 270 USD/month) according to the patient's yearly income. This support continues as long as the patients provide their yearly up-to-date data to the health center. Such a program has many benefits:

1. It lightens the patient's overall economic burden.
2. It makes it easier to receive expensive treatments such as biologics.
3. It facilitates yearly surveys of patients.

In addition to SDTRP, the government has organized and funded the "Research and Development Group for IBD," which consists of over 200 experienced IBD specialists. This group, currently directed by Prof. Watanabe, organizes multi-center clinical trials and basic research, and updates the national standard of diagnostic and therapeutic management of IBD. Also, members of this group currently participate in five ongoing worldwide trials co-operating with their counterparts in Europe and the US. Group members share their research progress at a semi-annual meeting, which makes it easy to spread the newest advances immediately to major facilities throughout our country.

Endoscopy is a standard modality for evaluation of IBD.

In Japan, well-trained and skilled experts in IBD frequently perform endoscopies on their patients. Since the development of balloon-assisted enteroscopy, the frequent use of endoscopy has been extended to the evaluation of small bowel lesions in Crohn's patients. Also, the aforementioned IBD specialist group is currently conducting a multi-center trial comparing target biopsy versus step biopsy for endoscopic surveillance of UC-related cancer. Thus, endoscopy is used as the most reliable modality to evaluate IBD in Japan. Furthermore, IBD experts in Japan are now trying to establish safe and effective endoscopic treatments for small bowel strictures in Crohn's.

Treatment of IBD in Japan has several unique features.

Although the severity and disease phenotype of IBD patients is similar between Japan and the western countries, the therapeutic approach is somewhat different, which is most well illustrated by the aggressive use of biologics in Japan. Among 154 Crohn's patients who visited our IBD center as regular follow-up for the past three months, 77 (50 percent) of them were maintained with anti-TNF agent. Furthermore, an additional 16 patients had been previously treated with biologics. Consistently,

a nationwide survey has shown that up to 40 percent of Crohn's patients in Japan have received biologic treatment. One reason for this high rate of biologic use may be that we do not have to withhold biologics for economic reasons, due to the SDTRP.

Furthermore, there are several unique options of IBD treatment that have been established in Japan. One example is "nutritional therapy." Total nutrition feeding has proved significant efficacy in achieving remission and maintenance of mild-to-moderate Crohn's. Another example is leukocyte apheresis, based on columns that can remove distinct populations of leukocytes and that has proven effective for UC. For severe patients, tacrolimus has proven effective to rescue steroid-refractory patients from colectomy, and is now becoming widely used. These treatments remain as an indispensable option for the treatment of IBD in Japan. Recently, we have also succeeded in transplanting primary intestinal cells cultured in vitro to repair damaged colitic mucosa. Such an innovative technique established from our basic research is now under development for use in IBD patients.

Future directions.

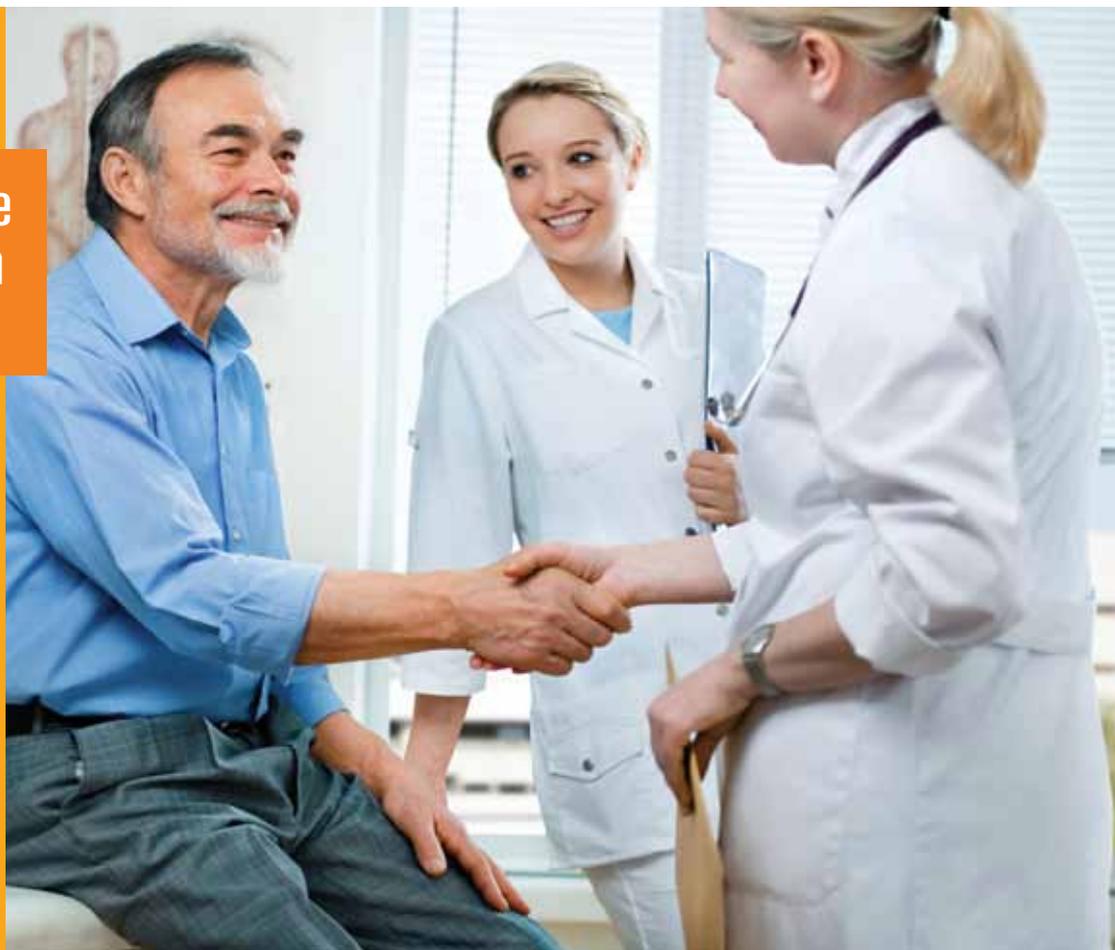
Taking advantage of the powerful support by the government-aided systems, we might be able to increase our future contribution to the worldwide improvement of IBD treatment, through high-quality clinical trials and innovative basic studies. ■



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