WINTER CME: THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

NORTHEAST FLORIDA MEDICINE

Published by the DCMS Foundation
Marking 162 Years of Local Organized Medicine

VOLUME 66, NO 4
WINTER 2015

INFLAMMATORY BOWEL DISEASE
A TEAM APPROACH TO TREATING STROKES

The stroke response team at Mayo Clinic in Jacksonville, FL, is skilled in rapid diagnosis and treatment of stroke, brain hemorrhage and other cerebrovascular and brain disorders.

So whether your patients need a proactive screening, a second opinion or emergency surgery, Mayo Clinic is your partner in delivering the best possible care when it’s needed most. For immediate referrals, call us at 800-634-1417.

- Full range of interventional treatment and surgery
- Complete diagnostic radiology services
- Dedicated Neuro ICU
- NIH-funded clinical trials
- Telestroke network
- Post-stroke care, case management and rehabilitation services

Certified as a Comprehensive Stroke Center by the Joint Commission and by the State of Florida.
A WAY TO MAKE MEDICINE EVEN MORE OF A MISSION.

There are opportunities for physicians to gain extraordinary experience serving part-time in America’s Navy Reserve. And all while maintaining a civilian practice. You can work in any of more than 30 specialty/subspecialty areas — from General Practice to Neurosurgery. Enjoy excellent pay and benefits — including the potential for additional specialty pay of up to $75,000.* And be part of a network that’s both patient-focused and world-class.

WANT TO LEARN MORE? CONTACT YOUR NAVY RESERVE MEDICAL RECRUITER TODAY.

(800) 342-8123  Jobs_nrd_jacksonville@navy.mil

*Contact a Navy Reserve Medical Recruiter for details. ©2012. Paid for by the U.S. Navy. All rights reserved.
8,000 patients treated • 200 papers published

Terk Oncology
& Center for Prostate Care

98% Cured

Terk Oncology achieves
the best published long-term Cure Rates

Where The Experts Go

For appointments please call: 904-520-6800

Dr. Mitchell Terk | Dr. Jamie Cesaretti | www.terkoncology.com

7017 AC Skinner Parkway, Jacksonville, FL 32256 | A division of Florida Physician Specialists

Primary Care Physicians (PCPs) play an important role in the management of patients with IBD. They should know when to suspect and refer patients with IBD, how to screen and treat for bone loss, update all vaccinations, screen and treat for depression and anxiety, when to consider screening for self-image, and how to monitor and treat nutritional deficiencies. They should also understand the role of NSAIDs, smoking and Clostridium difficile infections. PCPs are critical to optimizing patient care and outcomes.

Features

Advances in Inflammatory Bowel Disease
By Mark Fleisher, MD
Guest Editor

Advanced Endoscopy and Inflammatory Bowel Disease: Beginning of a New Era
By Ali Lankarani, MD

Out with the Old and In with the New? The Changing Approach to Colorectal Cancer Surveillance in Ulcerative Colitis
By Michael F. Picco, MD, PhD, FACG

Vaccination Recommendations for Patients with Inflammatory Bowel Disease
By Anh Trung Chau, MD

The Extraintestinal Manifestations of Inflammatory Bowel Disease
By John M. Petersen, DO, FACG, FACP

Surgical Management of Crohn’s Disease
By Anand S. Gupta, MD

Pancreatic Diseases in Patients with Inflammatory Bowel Disease
By Martha Arévalo, MD and Jose M. Nieto, DO, FACP, FACG, AGAF

Winter CME

The Role of a Primary Care Physician in the Management of Inflammatory Bowel Disease
By Bharat K. Misra, MD

Departments

6 From the Editor’s Desk
7 From the President’s Desk
8 From the Executive Vice President’s Desk
20 Residents’ Corner
22 Patient Page
Nowadays almost everything can be done online from purchasing a television, an airline ticket or clothing to earning a master’s degree without ever stepping onto a college campus. In the last 10 years, this transition has been swift and universally accepted. Despite this, approximately 40 percent of physicians continue to practice without electronic medical records. In an age when people can shop for groceries from their phone, millions still receive written medication prescriptions and have no way of communicating with their physician without picking up the phone. The reasons for not implementing some form of EMR range from the cost of the system to concerns over the implementation process and the amount of time necessary to research the proper system. These, of course, are legitimate issues but, in the end, the benefits will hopefully outweigh the initial drawbacks.

Benefits of EMR:

The obvious and most basic benefits associated with electronic medical records include the elimination of poor penmanship and the ease of chart access. Whereas the office staff may spend a considerable amount of time searching for paper charts, this is never a concern with an electronic system. Instead of writing a prescription in a hurry between patients, recording it in the chart, handing it to the patient who will then take it to the pharmacy for it to be dispensed, with a functional electronic system a prescription is sent to the pharmacy with one mouse click and with drug-to-drug interactions already checked. It not only saves the patient time, it appears safer as well. A 2010 *Journal of the American Medical Association* study suggests that there is a medication error rate reduction from 18.2 percent to 8.2 percent one year after implementing computerized electronic prescriptions.

Prior to EMR, a physician’s office would likely have to track down the results of common blood work because many times the laboratory would fail to send it in a timely fashion. With electronic records, typically the lab results are directly transferred into the patient’s chart and flagged when results are abnormal.

Vaccines have effectively had a positive impact on health care for the last 50-75 years. A 2001 study published in the New England Journal of Medicine suggests that computerized reminders about timely administration of influenza and pneumococcal vaccinations increased the appropriate use from practically 0 percent to 50 percent in hospitalized patients. A similarly designed study published in Arthritis also demonstrated positive results in the outpatient setting with an increase in pneumococcal vaccination rates from 19 percent to 41 percent.

Drawbacks of EMR:

There are certainly high costs associated with computerized medical records. A recent estimate suggests initial costs may be between $19,000 and $50,000 in a practice of three or fewer physicians. This does not include the cost of lost productivity during the implementation process. The initial cost is often followed up with ongoing maintenance for updating software and/or training new users. At the beginning, an EMR can disrupt work flow which can result in loss of productivity and increase the non-clinical responsibilities for the physician. A 2011 study suggests that during implementation physicians can spend 134 hours learning the system and this increases the non-patient based cost to over $10,000 per physician.

Moving Forward:

Electronic medical records certainly have positive and negative qualities both in the short and long-term. However, over the years, the systems have become more user-friendly and efficient. Just like every major cog in the United States economy, the practice of medicine is moving more towards a computerized electronic forum, without turning back. Hopefully, over time, we will be able to better quantify the benefits not just for the healthcare system but also for the physicians involved.

Electronic Medical Records: A Necessary Step
DCMS and the Future of Health in Northeast Florida

As 2015 nears its end, I would like to thank the Duval County Medical Society (DCMS) for the honor of serving as its president. It has truly been a privilege to serve and I hope that the next generation of DCMS members continues to fill the leadership ranks and support the DCMS mission of “helping physicians care for the health of our community.”

With every year that goes by, it is important to reflect on some of the initiatives that the DCMS has embarked upon to improve its abilities to support physicians and achieve its mission.

One great accomplishment this year has been the Leadership through Mentorship Task Force launching of the DCMS Leadership Academy. The DCMS Leadership Academy is a curriculum-based program in collaboration with the Brook’s College of Health at the University of North Florida (UNF) that will provide leadership training to physicians in Northeast Florida.

The program will kick off with an orientation luncheon at the University Club on February 12. This day will also include the first of two-part media training sessions. Three other leadership sessions are planned for March 11, April 8 and May 6 at the University of North Florida. The first session will cover the role of a physician leader. Topics include setting priorities, applying time management principles and defining your leadership purpose. This day will also include the second part of media training, giving physicians hands-on practice with media interviewing. The second session is on emotional intelligence and team building. Participants will learn various management styles, how to create high performance teams and how to reduce work-related stress, among other topics. The final session will cover strategic planning and culture change.

Enrollment in the first class is available until January 31, 2016 by calling 904-355-6561. The sessions will take place on four Fridays starting in February and ending in May 2016. The DCMS Leadership Academy naturally supports the DCMS mission because stronger leaders create a stronger, more impactful medical society.

In 2016, the DCMS is bringing back monthly membership meetings that will provide live continuing medical education (CME) sessions. Members will be able to enjoy these sponsored dinners with spouses or significant others. These meetings will not only provide CME credit, but help bring DCMS members together and increase social and professional contact and collaboration.

During 2015, DCMS led another initiative to improve the care of stroke in our community. After an effort that involved hospitals, emergency room leaders, emergency response providers and stroke centers in the area, DCMS explored the viability of a consensus conference on the management of stroke. As a result, our Board of Directors has decided to change its approach and develop an annual Future of Health symposium that would focus on stroke in its first meeting.

The purpose of the Future of Health symposium is to continue dialogue and develop venues to better improve the care of patients in our community. DCMS can be the independent and honest broker that brings all stakeholders to the table in developing meaningful health care initiatives.

The DCMS Foundation is also embarking on an exciting project that will benefit Northeast Florida. After a comprehensive analysis of the feasibility and potential, the Foundation will soon unveil its plans. Your support will be important in moving this effort forward.

If you are interested in participating in the DCMS Leadership Academy, please email our Communications Coordinator, Kristy Wolski, at kristy@dcmsonline.org. I encourage you to participate. I truly believe that you receive most when you invest time and effort into strengthening your own community. Please do not hesitate to share your suggestions and thank you for your support!

Dr. Assar is Aetna’s Medical Director for North Florida. Articles or opinions provided by Dr. Assar do not necessarily reflect the views of Aetna.
Are You Getting the Most Out of Your Membership?

The Duval County Medical Society is the oldest medical association in the state of Florida. It’s also the second largest professional organization in Jacksonville. So the Society is not a secret. Nearly 2,000 physicians enjoy the benefits of membership, including *Northeast Florida Medicine* which you are reading right now. Did you know that *Northeast Florida Medicine* is the only peer-reviewed medical journal produced by Florida physicians for Florida physicians?

If you didn’t, that’s OK.

There’s a ton of value packed in your DCMS Membership. For example, did you know that you have free access to all mandatory CME required in Florida? Did you know that you’re eligible for a five percent rate reduction on the most popular medical malpractice insurance in the state of Florida? And did you know that you have access to a free consultation on payment disputes?

These are just a few of the benefits that DCMS members enjoy every day. To make the most of your member benefits, make sure to keep your 2016 DCMS Directory handy. It will be arriving at your home or office very soon. This Directory (free for DCMS Members) not only provides you a comprehensive guide to physicians and their practices across a five-county region in northeast Florida, it also gives you a complete breakdown of all of the benefits available to you.

Here are a few highlights:

- Monthly CME dinners for you and a guest (NEW in 2016)
- Discounts at hundreds of local businesses with the DCMS MEMBERCARD (NEW in 2016)
- Discounted rates for a variety of services including web hosting, travel insurance, CE Broker and more
- Access to the Payer Provider Hotline: a FREE consultation on legal reimbursement questions: 888-455-7702
- Inclusion in the DCMS Directory and a complimentary copy
- Access to the ONLY County Medical Society dinner that occurs every year with the President-elect of the American Medical Association
- The opportunity to publish a Doctors on Call article in *The Florida Times-Union*

Those are just some of the member benefits that impact you and your practice. However, at its core, the DCMS is also a place for physicians who are passionate about healthcare and the delivery of healthcare in this community to play their part. The DCMS has several committees that are always looking for new physicians to aid the DCMS Mission: Helping physicians care for the health of our community.

We know that regulatory burdens are one of the most frustrating parts of being a physician today. That’s why the DCMS works to represent physicians in Tallahassee. Complex issues such as scope of practice expansion, telemedicine, Medicaid expansion and restrictions on controlled substance prescribing continue to be hot topics year after year. We know that taking care of your patients is your number one concern, so we take your concerns directly to Tallahassee.

DCMS is also vested in nurturing the next generation of leaders in the Society, the community, and across the country. DCMS members have served as the president of organizations ranging from the Florida Medical Association, American Medical Association, and even the World Medical Association! As a promise to continue developing those future leaders, DCMS Members can participate in the DCMS Leadership Academy. The Leadership Academy is a four-session course that will prepare you to become a stronger leader in your current position or as a leader in the medical community. The program kicks off this February.

It doesn’t stop there. In the coming months you will hear about even more exciting developments from the DCMS and the Duval County Medical Society Foundation. Together, with you and your colleagues, we will continue to work to improve the health of our community.

To learn more about getting involved, please visit the member benefits page on our website: www.dcmsonline.org. You can also call our office at (904) 355-6561 or email me at bcampbell@dcmsonline.org.
UC IS OVERWHELMING TREATMENT SHOULDN'T BE
You **prescribe** SIMPONI®.
Your patients **get** SIMPONI®.

For your commercially insured patients:

![Diagram showing the process of SIMPONI® prescription and access](image)

**SIMPONI® First-Line Access** provides SIMPONI® (golimumab) to your eligible patients if coverage is delayed or denied.

Only available to commercially insured patients prescribed SIMPONI® 100 mg. Not valid for patients enrolled in Medicare, including Medicare Part D, TriCare, VA, or Medicaid.

Your patients receive SIMPONI® through the current calendar year with an option for re-enrollment.

- Patients or healthcare providers can repeat the enrollment process and re-enroll in the program for another year
- Late-year applicants (November-December) are approved through the following calendar year

Get your patients started today: visit SimponiFirst.com

**SELECTED IMPORTANT SAFETY INFORMATION**

Serious and sometimes fatal side effects have been reported with SIMPONI®, including infections due to tuberculosis, invasive fungal infections (eg, histoplasmosis), bacterial, viral, or other opportunistic pathogens. Prior to initiating SIMPONI® and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection. Lymphoma, including a rare and fatal type called hepatosplenic T-cell lymphoma (HSTCL), and other malignancies, can occur in adults and children, and can be fatal. Other serious risks include melanoma and Merkel cell carcinoma, heart failure, demyelinating disorders, hypersensitivity reactions, and hepatitis B reactivation. Prior to initiating SIMPONI®, patients should be tested for hepatitis B viral infection.

Please see the Brief Summary of Prescribing Information on the preceding pages.

© Janssen Biotech, Inc. 2015 03/15 03299-150413
In adults with moderately to severely active ulcerative colitis (UC) who are corticosteroid dependent or have failed conventional therapy, the injection experience she wants, proven efficacy she needs\(^1\)

**SIMPONI\(^\circledR\) has half the injections of Humira\(^\circledR\)\(^2\)**

SIMPONI\(^\circledR\) (golimumab) - 15 Injections (1st year)

Humira\(^\circledR\) (adalimumab) - 30 Injections (1st year)

This is not intended to compare the safety, effectiveness, or uses of these treatments. Please refer to each product’s Prescribing Information for recommended dosing and administration. Humira\(^\circledR\) is a registered trademark of AbbVie Inc.

Most common adverse reactions for SIMPONI\(^\circledR\) are upper respiratory tract infection, nasopharyngitis, and injection-site reactions.

SIMPONI\(^\circledR\) is indicated in adults with moderately to severely active ulcerative colitis (UC) for inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, and achieving and sustaining clinical remission in induction responders who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine.

\(^*\)The safety and efficacy of SIMPONI\(^\circledR\) in UC were established in a Phase 2/3 induction study and a Phase 3 maintenance study.\(^4\)

**IMPORTANT SAFETY INFORMATION FOR SIMPONI\(^\circledR\) (golimumab)**

**SERIOUS INFECTIONS**

Patients treated with SIMPONI\(^\circledR\) are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue SIMPONI\(^\circledR\) if a patient develops a serious infection.

Reported infections with TNF blockers, of which SIMPONI\(^\circledR\) is a member, include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before SIMPONI\(^\circledR\) use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI\(^\circledR\) use.
SmartJect® autoinjector

Designed to keep the needle out of sight

Injection-site reactions

In the PURSUIT Induction study, 3.4% of SIMPONI®-treated patients (n=25734) reported injection-site reactions vs 1.5% of placebo patients (n=5330). Injection-site reactions included redness, swelling, itching, pain, bruising, and tingling.1,3

SIMPONI® injection schedule for UC: Week 0: 2 (100-mg) injections. Week 2: 1 (100-mg) injection. Week 6 and every 4 weeks thereafter: 1 (100-mg) injection.

SIMPONI® is intended for use under the guidance and supervision of a physician. Patients may self-inject SIMPONI® after physician approval and proper training.

Prior to initiating SIMPONI® and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection. Prior to initiating SIMPONI®, patients should be tested for hepatitis B viral infection.

Learn what SIMPONI® can offer your UC patients at InjectionExperience.com

- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with SIMPONI® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Do not start SIMPONI® in patients with clinically important active infections, including localized infections. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy, who are on treatment for latent TB, or who were previously treated for TB infection.

(CONTINUED ON NEXT PAGE)
IMPORTANT SAFETY INFORMATION FOR SIMPONI® (golimumab) (CONT’D)

Risk of infection may be higher in patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant therapy. Other serious infections observed in patients treated with SIMPONI® included sepsis, pneumonia, cellulitis, abscess and hepatitis B infection.

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers of which SIMPONI® is a member. Approximately half the cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of malignancies, including rare malignancies usually associated with immunosuppression and malignancies not usually observed in children or adolescents. Malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

In the controlled portions of clinical trials of all TNF-blocking agents including SIMPONI®, more cases of lymphoma have been observed among patients receiving TNF-blocking treatment compared with control patients. In the Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS) clinical trials, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI® group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In clinical trials, the incidence of malignancies other than lymphoma was not increased with exposure to SIMPONI® and was similar to what would be expected in the general population. In controlled and uncontrolled portions of the Phase 2/3 studies in ulcerative colitis (UC) with a mean follow-up of approximately 1 year, there were no cases of lymphoma with SIMPONI®. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. The risks and benefits of TNF-blocker therapy should be considered prior to initiating therapy in patients with a known malignancy or who develop a malignancy.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers. These cases have had a very aggressive disease course and have been fatal. Nearly all reported cases have occurred in patients with Crohn’s disease or UC, and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. A risk for the development for HSTCL in patients treated with TNF blockers cannot be excluded.

Melanoma has been reported in patients treated with TNF-blocking agents, including SIMPONI®. Merkel cell carcinoma has been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

HEPATITIS B REACTIVATION

The use of TNF-blocking agents including SIMPONI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consult a physician with expertise in the treatment of hepatitis B before initiating TNF-blocker therapy. Exercise caution when prescribing SIMPONI® for patients identified as carriers of HBV and closely monitor for active HBV infection during and following termination of therapy with SIMPONI®. Discontinue SIMPONI® in patients who develop HBV reactivation, and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of SIMPONI®, and monitor patients closely.

HEART FAILURE

Cases of worsening congestive heart failure (CHF) and new-onset CHF have been reported. Exercise caution and monitor patients with heart failure. Discontinue SIMPONI® if new or worsening symptoms of heart failure appear.

DEMYELINATING DISORDERS

TNF-blocking agents, of which SIMPONI® is a member, have been associated with rare cases of new-onset or exacerbation of demyelinating disorders, including multiple sclerosis (MS) and Guillain-Barré syndrome. Cases
of central demyelination, MS, optic neuritis, and peripheral demyelinating polyneuropathy have rarely been reported with SIMPONI®. Exercise caution in considering the use of SIMPONI® in patients with these disorders. Consider discontinuation if these disorders develop.

HEMATOLOGIC CYTOPENIAS
There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving SIMPONI® in clinical trials. Additionally, aplastic anemia has been reported in patients receiving TNF-blocking agents, of which SIMPONI® is a member. Exercise caution when using SIMPONI® in patients who have or had significant cytopenias.

USE WITH OTHER DRUGS
The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore the use of SIMPONI® in combination with these products is not recommended. Care should be taken when switching from one biologic to another since overlapping biological activity may further increase the risk of infection. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. The concomitant use of SIMPONI® with biologics approved to treat RA, PsA, or AS is not recommended because of the possibility of an increased risk of infection.

VACCINATIONS/ThERAPEUTIC INFECTIOUS AGENTS
People receiving SIMPONI® can receive vaccinations, except for live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. Administration of live vaccines to infants exposed to SIMPONI® in utero is not recommended for 6 months following the mother’s last SIMPONI® injection during pregnancy due to an increased risk of infection. It is recommended that therapeutic infectious agents not be given concurrently with SIMPONI® due to the possibility of clinical infections, including disseminated infections.

HYPERSENSITIVITY REACTIONS
Serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported with SIMPONI®, some occurring after the first dose. If an anaphylactic or other serious allergic reaction occurs, discontinue SIMPONI® immediately and institute appropriate therapy.

ADVERSE REACTIONS
The most serious adverse reactions were serious infections and malignancies.
Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of patients treated with SIMPONI® as compared with 6% and 5% of patients in the control group, respectively. The rate of injection-site reactions was 6% with patients treated with SIMPONI® compared with 2% of patients in the control group.
In the Phase 2/3 trials in UC evaluating SIMPONI®-treated patients, no new adverse drug reactions were identified, and the frequency of adverse drug reactions was similar to the safety profile observed in patients with RA, PsA, and AS.

Please see the Brief Summary of Prescribing Information on the following pages.

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with SIMONPI® are at increased risk for developing serious infections that may lead to hospitalization or death (see Warnings and Precautions). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue SIMONPI® if a patient develops a serious infection.

Respiratory tract infections with TNF-blockers, of which SIMONPI® is a member, include:

• Active tuberculosis, including reactivation of latent tuberculosis.
Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before SIMONPI® use and during therapy. Initiate treatment for latent TB prior to SIMONPI® use.

• Invasive fungal infections including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric antifungal therapy in patients at risk for invasive fungal infections who develop an Atypical Pneumonia or Systemic Illness.

• Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Consider the risks and benefits of treatment with SIMONPI® prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during treatment with SIMONPI®, including with and without concurrent use of methotrexate. Spondylitis SIMONPI® is indicated for the treatment of adult patients with active ankylosing spondylitis. Ulcerative Colitis SIMONPI® is indicated in adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or intolerance of oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response • improving endoscopic appearance of the mucosa during induction • inducing clinical remission • achieving and sustaining clinical remission in induction phase (see Clinical Studies: Phase 2a). No new WARNINGS AND PRECAUTIONS: Serious Infections Patients treated with SIMONPI® are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, viral, fungal, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMONPI® and these biologic products is not recommended (see Warnings and Precautions and Drug Interactions). Treatment with SIMONPI® should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with AIDS-related conditions, and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Consider the benefits of treatment with SIMONPI® to initiate therapy in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • who have a history of an opportunistic infection; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or • with underlying conditions that may impair their ability to mount an appropriate defense of therapy. In patients with AIDS-related necrosis who develop an Atypical Pneumonia, carefully monitor patients for the development of signs and symptoms of infection during and after treatment with SIMONPI®. Discontinue SIMONPI® if a patient develops a serious infection, an opportunistic infection, or sepsis. For a patient who develops tuberculosis during treatment with SIMONPI®, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy and closely monitor them.

Serious Infection in Clinical Trials In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMONPI®-treated patients and 1.2% of control-treated patients. In the controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.7 per 100 patient-years in SIMONPI®-treated patients and 4.9 per 100 patient-years in control-treated patients. The incidence of serious infections per 100 patient-years of follow-up was 5.7 per 100 patient-years in SIMONPI®-treated patients and 4.9 per 100 patient-years in control-treated patients. In the controlled Phase 3 trial through Week 6 of SIMONPI® induction in patients with rheumatoid arthritis, 1.9% of patients who received SIMONPI® induction and placebo during the maintenance portion of the UC trial. Serious infections in SIMONPI®-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection. Tuberculosis Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMONPI® and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMONPI®, assess if treatment for latent tuberculosis is needed; an induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG). Consider anti-tuberculosis therapy prior to initiation of SIMONPI® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended for any changes in therapy and for initiation of anti-tuberculosis therapy. Neither initiating anti-tuberculosis therapy nor excluding an individual patient. Cases of active tuberculosis have occurred in patients treated with SIMONPI® during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis. Assess for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection. Consider tuberculosis in the differential diagnosis in patients who develop a new active infection while receiving SIMONPI® during treatment, especially if they have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS, trials, the incidence of active TB was 0.23 per 100 patient-years in 2,274 SIMONPI®-treated patients and 0.06 per 100 patient-years in 2,040 placebo-treated patients, respectively. Cases of TB included pulmonary and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. In the controlled Phase 2/3 trial of SIMONPI® induction and 100 mg during the maintenance portion of the UC trial was 0.52 (95% CI: 0.11, 1.53). One case of TB was observed in the placebo maintenance group in a patient who received SIMONPI® intravenous (IV) maintenance. Invasive Fungal Infections If patients develop a serious systemic illness and they refuse or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Consider empiric antifungal therapy and take into consideration the risks for severe fungal infection and the risks of antifungal therapy while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. To aid in the diagnosis of fever of unknown origin, consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections. Hepatitis B Virus Reactivation The use of TNF-blockers including SIMONPI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronically hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants. All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for HBV surface antigen, consult with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMONPI®, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy reduces the risk of HBV reactivation in patients receiving TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following discontinuation of therapy. Monitoring for Hepatitis B Reactivation Monitoring of hepatitis B virus (HBV) DNA. Patients who develop abnormal ALT levels should be tested for HBV DNA, and if HBV DNA is positive, antiviral therapy should be started. Other patients should be closely monitored for signs and symptoms of HBV infection.
SIMPONI® (golimumab) - closely monitored during therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear. Demyelinating Disorders: Use of TNF-blockers, of which SIMPONI is a member, has been associated with cases of clinically isolated syndromes (CIS), multiple sclerosis (MS), and primary demyelinating disorders, including Guillain-Barre syndrome. Cases of demyelinating, optic neuritis, and peripheral demyelinating polyneuropathy have been treated with TNF-blockers. Risk of demyelinating disorders has been associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI and abatacept is not recommended (see Drug Interactions). Use with Anakinra Concurrent administration of anakinra (an interleukin-1-antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI, is not recommended (see Drug Interactions). Switching Between Biological Disease Modifying Anti-Rheumatic Drugs Care should be taken when switching from one biological product to another. The biological product should be selected based on the patient’s response to the previous biological product since over-lapping biological activity may further increase the risk of infection. Hematologic Cytopenias There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. In clinical trials, cases of pancytopenia, leukopenia, and thrombocytopenia were uncommon in SIMPONI-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI, in patients who have had significant cytopenias. Vaccinations/Therapeutic Infectious Agents SIMPONI is not recommended for use in patients with live vaccines, except for live vaccines. In patients receiving anti-TNF therapy, limited data are available on the response to live vaccination, or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. Therapeutic Infectious Agents Other uses of therapeutic infectious agents (e.g., BCG, as a prophylactic measure) should be considered in patients treated with TNF-blockers. In the group of patients with vasculitis, a proportion of patients treated with placebos had an increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI-treated and placebo-treated patients, the proportion of patients with a response to pneumococcal vaccine were lower among patients receiving MTX compared with patients not receiving MTX. The data suggest that SIMPONI does not suppress the humoral immune response to the pneumococcal vaccine. Hypersensitivity Reactions In post-marketing data, serious allergic reactions (including anaphylactic reaction) have been reported following SIMPONI administration. Some of these reactions occurred after the first administration of SIMPONI. If an anaphylactic or other serious allergic reaction occurs, administration should be discontinued immediately and appropriate therapy instituted. 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 may not be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The safety data below are based on 5 pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Trials RA-1, RA-2, RA-3, PsA, and AS) (see Clinical Studies). These 5 trials included 1,059 control-treated patients and 1,610 SIMPONI-treated patients. During 1008 with RA, 292 with PsA, and 116 with AS. The safety data from 1233 SIMPONI-treated patients with ulcerative colitis from 3 pooled, randomized, double-blind, controlled Phase 2 trials are also described below (Trials UC-1, UC-2, and UC-3) (see Clinical Studies). The proportion of patients with adverse reactions requiring discontinuation of SIMPONI in the combined Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI-treated patients and 3% for placebo-treated patients. The most common adverse reaction leading to discontinuation of SIMPONI in the controlled Phase 3 trials was reactivation of hepatitis (0.2 vs 0.6%) and anemia (0.3 vs 0%). The most serious adverse reactions were: • Serious Infections (see Warnings and Precautions) • Malignancies (see Warnings and Precautions) Adult respiratory distress syndrome and infections and neoplasms were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of SIMPONI-treated patients as compared with 6% and 5% of control-treated patients, respectively. Infections In controlled
Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI-treated patients compared to 25% of control-treated patients. For serious infections, see the Warnings and Precautions section (see Warnings and Precautions). In the controlled Phase 3 trial of SIMPONI induction through Week 6 in UC, the rates of infections were similar in SIMPONI 200/100 mg-treated patients and placebo-treated patients, or approximately 12%. Through Week 60, the incidence per patient year of infections in similar patients who received SIMPONI induction and 100 mg placebo was compared with control patients who received SIMPONI induction and placebo during the maintenance portion of the UC trial. 

Demethylating Disorders In the controlled Phase 2/3 trial of SIMPONI induction through Week 8, no cases of demethylona were observed in SIMPONI 200/100 mg-treated patients or placebo-treated patients. Through Week 52, the incidence of demethylona was observed in the SIMPONI 200 mg group in the SIMPONI 200 mg group in the placebo maintenance group in a patient who received SIMPONI 400/200 mg during induction. 

Liver Enzyme Elevations There have been reports of severe hepatic injury, including acute liver failure, in patients treated with TNF antagonists. In a phase 3 trial of SIMPONI in patients with RA, PsA, and AS through Week 16, ALT elevations ≥ 5 ULN occurred in 0.2% of control-treated patients and 0.7% of SIMPONI-treated patients and ALT elevations ≥ 5 x ULN occurred in 2% of control-treated patients and 2% of SIMPONI-treated patients. Since most of the patients in the Phase 3 trials for RA, PsA, and AS were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX, the relationship between SIMPONI and liver enzyme elevation is not clear. In Phase 2/3 UC trials, the incidence of ALT elevations ≥ 5 x ULN was similar in SIMPONI-treated patients and placebo-treated patients (1% each), with an average duration of 46 weeks and 18 weeks, respectively. ALT elevations ≥ 5 x ULN occurred in 2% of SIMPONI-treated patients compared with 1.5% of placebo-treated patients with an average duration of follow-up of 46 weeks and 18 weeks, respectively. 

Infections and Infestations: Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinopharyngitis) was reported in 16%, 13%, 16%, 13%, viral infections (e.g., influenza and herpes) was reported in 1%, 2%, 1%, 2%, 1%, and other infections (e.g., infections of lungs, breast, skin, and subcutaneous tissue infections 2%, 1%, 1%, 1%, 1%, 1%, and unspecified infections) 1%, 1%, 1%, 1%, 1%, 1%, respectively. 

Less common clinical trial adverse drug reactions Adverse drug reactions that occurred <1% in SIMPONI-treated patients during the SIMPONI clinical trials that do not appear in the Warnings and Precautions section included the following events listed by system organ class: Infections and infestations: Septic shock, atypical mycobacterial infection, pyelonephritis, arthralgia, infectious and parasitic diseases. 

Drug Interactions: Concomitant use of SIMPONI with other biologic or TNF antagonists is not recommended. Use of other concomitant immunosuppressive agents, such as cyclosporine or methotrexate, may increase the risk of infections. 

Biological Products for RA, PsA, and/or AS An increased risk of serious infections has been seen in clinical trials of other TNF-alpha inhibitors used in combination with anti-TNF or anti-IL-17 agents. Combined use of SIMPONI with other biologic or TNF antagonists is not recommended. Use of other concomitant immunosuppressive agents, such as cyclosporine or methotrexate, may increase the risk of infections. 

Live Vaccines/Therapeutic Infectious Agents Live vaccines should not be given concurrently with SIMPONI (see Warnings and Precautions). 

Cytokine P450 Substrates The formation of CYP3A4 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic treatment with SIMPONI. 

USE IN SPECIFIC POPULATIONS: Pregnancy Pregnancy Category B – There are no adequate and well-controlled trials of SIMPONI in pregnant women. Because animal reproduction studies are not always predictive of human response, and because animal reproductive studies are not always predictive of human response, and because animal toxicity studies do not always predict safe human therapeutics, it is unknown whether SIMPONI can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI should be used during pregnancy only if clearly needed. An embryofetal developmental and reproductive toxicity study was performed in pregnant rats, and the fetuses were treated subcutaneously with golumub in the first trimester with doses up to 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MRHD) and has revealed evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to simponi during gestation. In this study, simponi exposure to golumub produced no developmental defects to the fetus. A pre- and postnatal developmental study

SIMPONI® (golimumab)
was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximum steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants. IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of infants born to patients treated with these antibodies. Since SIMONI is an IgG antibody, infants born to women treated with SIMONI during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMONI in utero is not recommended for 6 months following the mother’s last SIMONI injection during pregnancy (see Warnings and Precautions). Nursing Mothers It is not known whether SIMONI is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMONI, 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. In the pre- and postnatal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations. Pediatric Use Safety and effectiveness of SIMONI in pediatric patients less than 18 years have not been established. Geriatric Use In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMONI-treated patients ages 65 or older (N = 155) compared with younger SIMONI-treated patients. In UC, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMONI. Overdosage: In a clinical trial, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMONI without serious adverse reactions or other significant reactions. The highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000 mg of SIMONI. There were no SIMONI overdoses in the clinical trials. Patient Counseling Information: See FDA-approved patient labeling (Medication Guide and Instructions for Use) Patients should be advised of the potential benefits and risks of SIMONI. Physicians should instruct their patients to read the Medication Guide before starting SIMONI therapy and to read it each time the prescription is renewed. Infections Inform patients that SIMONI may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation. Malignancies Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMONI. Allergic Reactions Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringes in the prefilled SmartJect autoinjector contains dry natural rubber (a derivative of latex). Other Medical Conditions Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cystopenia, or psoriasis. Instructions for Safe Administration The first self-injection should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer SIMONI, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of SIMONI. Advise the patient to read the FDA-approved Instructions for Use and provide the following instructions to patients: • Prior to use, remove the prefilled syringe or the prefilled SmartJect autoinjector from the refrigerator and allow SIMONI to sit at room temperature outside of the carton for 30 minutes and out of the reach of children. • Do not warm SIMONI in any other way. For example, do not warm SIMONI in a microwave or in hot water. • Do not remove the prefilled syringe needle cover or SmartJect autoinjector cap while allowing SIMONI to reach room temperature. Remove these immediately before injection. • Do not pull the autoinjector away from the skin until you hear a first “click” sound and then a second “click” sound (the injection is finished and the needle is pulled back). It usually takes about 3 to 6 seconds but may take up to 15 seconds for you to hear the second “click.” If the autoinjector is pulled away from the skin before the injection is completed, a full dose of SIMONI may not be administered. • A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique of proper syringe and needle disposal, and be advised not to reuse these items.

Harsham, PA 19044 1-800-JANSSEN (1-800-526-7738)
US License No. 1804 Revised: 12/2014 022953-141204
Advances in Inflammatory Bowel Disease
By Mark Fleisher, MD

The field of inflammatory bowel disease is mostly uncharted territory. Like many questions in life, the two points of greatest interest are usually the least understood. I am referring to the beginning and the end. We are just starting to figure out how IBD begins. We are also trying to figure out a cure. It is in this setting that the study of inflammatory bowel disease is so humbling. It is hard to be an expert in a field where you cannot tell a patient how they got the illness and how they can get rid of it. However, we are making huge advances. The field is exploding with new medications. Gone are the days when all we had were steroids and mesalamine. Now, physicians are able to offer something else to patients. It is called hope.

Cognizant that most of our readers are either approaching middle age or deep in the throes of it, the question begs itself, “How did I get here?” This is the question regarding science itself. If the medications we had were perfect, then no new medications would be needed. However, that has not been the case with inflammatory bowel disease. Meta-analysis studies have shown that mesalamine-based products are all pretty much equivalent. The absolute reduction of risk for 5ASA products is approximately 25 percent better than placebo. However, this is only in mild to moderate disease. In more advanced disease, the 5ASA products are almost futile. Therein lies the paradox. The majority of patients with inflammatory bowel disease do not present with mild to moderate disease. They present mostly with moderate to severe disease. As such, a giant cohort of patients are offered medications that are doomed to fail. There was a study a long time ago that stated that perhaps 5ASA products might have a chemotherapeutic effect. However, a more recent study states this may not be the case either. And yet even more studies suggest that they might. As such, it is unclear what the role of 5ASA products are in the majority of IBD patients. Moreover, another study revealed that once a patient with inflammatory bowel disease has received steroid therapy, the efficacy of 5ASA products becomes nil.

Next came immunotherapy. Medications including azathioprine and methotrexate serve to staunch the unrelenting cascade of the immune system by inhibiting lymphocyte activity. However, the risks of immunotherapy are numerous. They include, but are not necessarily limited to, the following: nausea, vomiting, fever, hair loss, pancreatitis, hepatitis, drop in white blood cell count and lymphoma. Moreover, these medications only work perhaps 35 percent of the time.

Then came a beacon of hope. A new day dawned as biologic therapies began to take hold. Starting with infliximab and now refined with vedolizumab, physicians are starting to notice that there is an incredible overlap between seemingly unrelated illnesses. People with psoriasis had severe joint pains. People with Crohn’s disease had extraintestinal manifestations such as, at times, psoriasis. IBD patients had joint pains and many of them had positive rheumatoid factors and positive antinuclear antibody assays. In essence, the field of inflammatory bowel disease is just a subsection of the field of immunology. We noticed that an earlier application of more advanced therapy in patients with rheumatoid arthritis could change their future. These patients were treated with disease modifying anti-rheumatologic drugs (DMARD). It turns out that the earlier you apply biologic drugs the less likely the patient will develop deleterious and irrevocable consequences. Actually, this is not a surprise. The Architect of the human body is a genius. The axiom “time is tissue” is universally applicable. The longer you have reflux disease that is untreated the more likely you will develop Barrett’s esophagus and potentially esophageal cancer. The longer you have low blood flow to your brain as a stroke evolves the more likely you will have permanent consequences to the myocardium. And so it is with inflammatory bowel disease. The longer you have unabated inflammatory changes of the GI tract the more likely you will have immutable consequences in the form of perhaps a fistula or an abscess or a stricture and the more likely you will have intractable disease that will not be amenable to medical therapy.

The purpose of this issue of Northeast Florida Medicine is to give a cursory overview of numerous subtopics of inflammatory bowel disease. However, if the only thing you take out of this edition is the fact that time is tissue and that tissue is the issue, then we have done our job. Enjoy.

References
St. Vincent’s Family Medicine Residency in Jacksonville, Florida

By Meredith Riddle, DO, MS

About Us

St. Vincent’s Family Medicine Residency Program (SVFM) in Jacksonville, Florida has been training successful and compassionate physicians since 1972. SVFM physicians are known for providing complete care to a variety of patients, from expectant mothers and their newborns to elderly patients and their families. SVFM is dually accredited by the Accreditation Council of Graduate Medical Education (ACGME), training both MDs and DOs. St. Vincent’s currently educates 30 residents per year, with 10 residents in each of three classes. Residents come from all over the country with a variety of interests including Women’s Health, Sports Medicine, Obstetrics, Dermatology, Integrative Medicine, Rural Medicine and Pediatrics. The program provides residents access to a variety of facilities for training, along with benefits from affiliations with Ascension Health, Wolfson Children’s Hospital, Florida State University, the University of South Florida and NOVA Southeastern University. SVFM is proud to have multiple board-certified family medicine doctors on staff full-time as attending physicians, as well as a pediatrician, two OB/GYNs, and a clinical psychologist who all teach residents and continue their own panel of patients.

Our Home

St. Vincent’s Medical Center has three locations in the Jacksonville area: Riverside, Southside and Clay County. St. Vincent’s Riverside (SVR) is the home hospital for the residency program and is part of Ascension Health, the country’s largest non-profit Catholic health system. SVR is a 538-bed hospital that serves as a valuable training center with state-of-the art technology. For example, OB clinical simulators are used regularly to provide a beneficial experience delivering babies in high-risk situations. Also, up-to-date electronic medical records facilitate efficient communication between physicians, specialists and patients. Residents often find themselves in numerous locations during their training, including the newest 40-patient room Family Medicine Center which opened in 2004 and the associated nursing home St. Catherine’s Labouré Manor, both of which are adjacent to the hospital.
Giving Back

SVFM is proud to partner with the philanthropic tradition of St. Vincent’s HealthCare Foundation, a non-profit organization founded in 1982 dedicated to serving the community of Jacksonville. Residents and faculty alike are committed to participating in various community service and outreach projects in the area. For example, residents travel to various parts of Jacksonville and surrounding counties each week as part of The Mobile Health Outreach Ministry at St. Vincent’s to provide free care to patients who are unable to reach the facilities. This mobile unit also visits area schools year-round, offering free school and sports physicals to students. St. Vincent’s residents and attending physicians also care for patients of The Way Clinic, a free medical clinic in southern Jacksonville. Residents have even continued care of The Way Clinic patients by delivering babies of their OB patients at St. Vincent’s Medical Center. In addition, SVFM participates in many community activities. Perhaps most notably, SVFM promotes literacy in Jacksonville’s children by sponsoring the annual “Read and Romp” event each fall. This beloved community activity was originally started by a former St. Vincent’s resident 12 years ago, and has become a tradition in community education. The residency has also recently partnered with a local elementary school where residents will serve as mentors to the students throughout the year to promote life-long learning.

Leaders in Family Medicine

In addition to receiving complete training and education, many residents participate in leadership activities outside of St. Vincent’s. For example, one of our third year residents Dr. Sally Tran is currently the Resident Secretary-Treasurer for the Florida Academy of Family Physicians. SVFM residents also participate regularly in research projects which have earned state-wide attention. In the past year, graduated resident Dr. Elisa Pujals won first place in the poster competition at the Florida Academy of Family Physicians for her work in reducing hospital re-admission rates. Also in the past year, her classmate Dr. Leah Robinowitz won the NOVA CEME Resident Research Initiative Award based on her work with the Gardasil HPV vaccine.

Our Future

After completing the 3-year residency, SVFM residents pursue many areas of Family Medicine in urban, suburban and rural locations. Several physicians have gone on to complete 1-year OBGYN fellowships for extra training. Some graduates have continued their training in the armed forces, providing care to our nation’s heroes. Others have gone on to take part in international work. Still other graduates have made a home at St. Vincent’s and are currently attending physicians teaching each new class of residents. Overall, St. Vincent’s Family Medicine residency program strives to promote quality, compassionate healthcare for the Jacksonville area while giving back to the community. To learn more about the SVFM, please visit the residency website at www.svresidency.com.
Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder potentially affecting any portion of the gastrointestinal tract from the mouth to the anus. It is characterized by relapses and remissions and afflicts an estimated 500,000-2,000,000 people in the United States. The incidence of IBD is approximately equal in men and women. Most research has found the age of onset in adolescence and young adulthood, although there is a second peak incidence between the ages of 50 and 60.

IBD is classified as two major disease entities:

- **Ulcerative colitis (UC)** is mucosal inflammation that affects only the colon; it may involve the entire colon or only the distal colon/rectum. The severity of the inflammation can vary. Bloody diarrhea associated with mucosal inflammation is a classic symptom. Other symptoms include urgency, tenesmus, weight loss, fatigue, fever and night sweats.

- **Crohn's disease (CD)**, in contrast to UC, can affect any segment of the gastrointestinal tract. It most often presents in the ileum (ileitis), the ileum and the colon (ileocolitis) or colon alone (Crohn's colitis). Patients with CD typically have diarrhea, abdominal pain and weight loss; bleeding also often occurs. Although exacerbations and remissions are difficult to predict, nearly all patients experience a recurrence within 10 years of the first episode.

Extraintestinal Manifestations:

- Mouth sores may develop during flares of Crohn's disease or ulcerative colitis. These lesions are most commonly between the gums and lower lip or on the sides and underneath the tongue. These lesions are typically painful.

- Skin lesions, most commonly affecting the lower extremities, may occur.

- Eye inflammation, known as uveitis or scleritis, occurs in up to five percent of those with Crohn's disease or ulcerative colitis. The symptoms of uveitis include floaters in the vision, eye pain, and sensitivity to light. Scleritis is manifested by burning and itching of the affected eye (one or both eyes may be affected).

- Anal disease is more common in Crohn's disease than ulcerative colitis.

- Liver disease, specifically a condition known as primary sclerosing cholangitis (PSC), is increased in inflammatory bowel disease, in particular ulcerative colitis. PSC may also result in symptoms such as yellowing of the skin (jaundice), eyes (scleral icterus) and itching. Eventually PSC may result in liver failure.

Management Strategies

There are numerous treatment approaches to inducing and maintaining remission in patients with IBD. These treatments focus on suppressing the inflammation involved in the disease process. Your physician will discuss this with you in more detail.

References


Reprinted with permission from Mark Fleisher, MD, Borland-Groover Clinic. For more information contact: research@bgclinic.com.
Inflammatory Bowel Disease

Endoscopy in Diagnosis of IBD

One of the most important components in diagnosis of IBD is the information gathered from endoscopy. Location and pattern of inflammation, in addition to the shape, depth and appearance of the ulcerations, are some of the information gathered during endoscopy that helps in accurate diagnosis. Endoscopic biopsy, although rarely definitive in IBD, can help to rule out other disorders. Normal mucosal biopsies effectively exclude active IBD.

In ulcerative colitis (UC), inflammation almost always starts proximal to the anal verge and extends proximally in a continuous, confluent and concentric fashion. In comparison, Crohn’s Disease (CD) inflammation typically has a patchy distribution with skipped lesions (areas of inflammation interposed between normal appearing mucosa). Rectal sparing has been described in children presenting with UC prior to treatment. In adults with UC a normal or patchy inflammation in the rectum is more likely due to previous topical therapy.

Mucosal ulcerations in CD can be longitudinal, linear, or appear as multiple aphthous ulcers. In contrast, ulcers in UC tend to be more superficial. Strictures are exceedingly rare in UC and should raise the possibility of CD or underlying malignancy. None of the endoscopic features are specific for UC or CD. Biopsies taken from the edges of ulcers increase the chance of detecting granulomas, which are pathognomonic in CD.

Upper Gastrointestinal endoscopy is mandatory in pediatric patients with suspected IBD to confirm the diagnosis of CD. In adults, there are no specific recommendations regarding performance of upper GI endoscopy at the time of diagnosis. Upper GI endoscopy may be important in establishing diagnosis of Crohn’s disease, to assess disease extension and severity, and to aid in tailoring the therapy. Also, CD patients with dyspepsia, abdominal pain and vomiting would benefit from upper GI endoscopy. Finally, upper GI endoscopy is mandatory in patients with suspected concomitant coeliac disease.

Small bowel capsule endoscopy is instrumental in the early diagnosis of patients with suspected CD in the absence of involvement of the colon or terminal ileum. Small bowel capsule endoscopy is the most sensitive diagnostic test to detect early small bowel lesions and to exclude small bowel CD, even in patients with negative cross sectional imaging studies. In cases that cross-sectional imaging studies or small bowel capsule endoscopy are inconclusive, device-assisted enteroscopy may be performed to confirm the diagnosis of CD endoscopically and histologically.

Role of Endoscopy in IBD disease activity

Early achievement and maintenance of mucosal healing is considered to change the natural course of CD and prevent fistula and stricture formation. The same concept seems to offer a better prognosis compared to symptomatic control alone in patients with UC. Endoscopy is considered the gold-standard for evaluating disease activity and confirming mucosal healing. Other markers of active inflammation, such as increased faecal levels of calprotectin and lactoferrin, are less sensitive for mucosal healing and have been used as surrogates to monitor disease activity.
Multiple reproducible endoscopic scoring systems to measure the disease activity have been developed and validated. The most well-known scoring systems to determine the disease activity in CD are the Crohn’s Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn’s Disease (SES-CD). The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) are two of the widely used scoring systems for UC. Usefulness of implementing such endoscopic scoring systems in routine clinical setting has yet to be determined.

Therapeutic Endoscopy in IBD

Typical CD begins with a mucosal inflammatory pattern that over time develops into strictures or fistulas. The Vienna Classification describes three distinct groups of CD: inflammatory, stricturing and penetrating. Structuring disease is predominant in the terminal ileum and ileocolonic anastomosis or in the ileal pouch. Strictures are believed to be either inflammatory or fibrotic. Inflammatory strictures have the option of being treated by medical therapy.

The most common reason for surgery in CD is intestinal strictures. Surgical resection and stricturoplasty are the traditional means of treatment for patients that fail to respond to medical treatment. There is increasing evidence for endoscopic treatments as safe and effective alternatives to surgery in these patients.

A systematic review summarized the results of key studies of endoscopic balloon dilatation in CD. Overall, technical success was achieved in 86 percent of patients. The complication rates were mainly less than 5 percent. Endoscopic dilatation was successful in avoiding surgery at the end of the follow-up in 67 percent of patients who were included in this review. If the patients who had failed for technical reasons were excluded, the success rate measured by avoidance of surgery was up to 78 percent.

Re-dilatations may be required in up to 20 percent of patients at one year and up to 50 percent of patients by five years. These are comparable to the stricture recurrence rate of 45 percent at five years following surgical stricturoplasty. Device-assisted enteroscopy and dilatation of deep small bowel strictures and dilation of ileal pouch strictures are reported to be successful in expert hands.

Rectal pain and discharge can be due to rectal inflammation or a sign of perianal fistula in a patient with rectal CD. Approximately 25 percent of all patients with CD develop a perianal fistula. Identification of fistulae is difficult with digital rectal examination alone, or even with examination under anesthesia. Endoscopic ultrasonography (EUS) has been used in CD patients with rectal involvement to help with the detection of fistulae. EUS is more accurate than CT (82 percent versus 24 percent) or pelvic MRI (82 percent versus 50 percent) to discover perianal fistulae.

Primary Sclerosing Cholangitis (PSC) is a chronic, cholestatic liver disease characterized by inflammation and fibrosis of both intrahepatic and extrahepatic bile duct and leads to the formation of bile duct strictures. PSC is strongly associated with inflammatory bowel disease, mainly UC, and is often complicated by development of cholangiocarcinoma. Endoscopic retrograde cholangiography (ERC) assisted dilation and stent placement has been proven to be a safe and efficacious mode of treating primary sclerosing cholangitis-associated strictures. ERC can help with improvement of symptoms and cholestasis with a low rate of complications. The risk of cholangiocarcinoma after 10 years and 20 years of PSC is 9 percent and 19 percent respectively. Bile duct brushings, EUS-assisted fine needle aspiration and cholangioscopy are commonly used for tissue acquisition and diagnosis of PSC-associated cholangiocarcinoma.

Endoscopic mucosal resection (EMR) is an endoscopic technique developed for removal of sessile or flat neoplasms confined to the superficial layers (mucosa and submucosa) of the GI tract. EMR is typically used for removal of lesions smaller than 2 cm or piecemeal removal of larger lesions. In one study, EMR was used to remove 79 flat lesions with a recurrence rate of 2.4 percent at three years. No additional lesions were detected in a four-year follow-up period.

IBD and Colorectal Neoplasia Surveillance

The risk of CRC in IBD is increased with the duration and extent of disease. UC patients have a higher risk of developing colorectal cancer (CRC) than the general population. In the largest report of surveillance colonoscopy in patients with extensive UC, the cumulative incidence of CRC increased from 2.5 percent at 20 years to 10.8 percent at 40 years. A meta-analysis that included multiple large population-based studies reported the incidence of CRC to 2 percent at 10 years, 8 percent at 20 years, and 18 percent at 30 years of disease activity in UC patients.

Patients with terminal ileum Crohn’s have the same risk of CRC as the general population, but those with colonic Crohn’s have a relative risk (RR) of 5.6 (95 percent CI 2.1–12.2). The CRC risk appears to correlate with the extent and...
duration of colonic involvement.\textsuperscript{31} It is now believed that the risk of developing CRC in UC and CD is identical.\textsuperscript{32}

Traditionally, interval colonoscopies with random biopsies of normal mucosa and targeted biopsies of suspicious lesions have been recommended for dysplasia surveillance in patients with chronic colitis. Newer methods aimed at detecting dysplastic mucosa have been studied. High-definition white light endoscopy and enhanced magnification colonoscopy have been used to increase the yield in detecting dysplasia. Recent colitis surveillance studies showed that high-definition colonoscopy improved dysplasia detection compared to standard definition.\textsuperscript{33}

Chromoendoscopy is a dye-spraying technique that highlights the borders and surface architecture of neoplastic lesions (pit pattern). Chromoendoscopy helps in unmasking and delineating subtle lesions and aids in the differentiation of neoplastic and non-neoplastic tissue.\textsuperscript{34} With this method, random biopsies of apparently normal mucosa are of negligible additional value.\textsuperscript{35,36} Diagnostic yield of chromoendoscopy is comparable when methylene blue or indigo carmine are used as the contrast agent.\textsuperscript{37,38}

Chromoendoscopy has been compared to standard-definition endoscopy for detection of neoplasia in both IBD and non-IBD patients and has been shown to be superior.\textsuperscript{39} Another meta-analysis looked at the diagnostic accuracy of chromoendoscopy compared to histology and reported a sensitivity of 83.3 percent and specificity 91.3 percent for chromoendoscopy in detection of intraepithelial neoplasia.\textsuperscript{40} Several randomized studies suggest that advanced endoscopic imaging modalities may obviate the need for multiple random biopsies for dysplasia surveillance in IBD patients with chronic colitis.

Virtual chromoendoscopy technologies have been developed as an alternative to dye based chromoendoscopy. Virtual chromoendoscopy relies on the use of selective light filters and post-image processing techniques to highlight vessel and crypt architecture by altering the light that is emitted to the mucosa. Commercially available virtual chromoendoscopy techniques are narrowband imaging (NBI; Olympus, Tokyo, Japan), i-scan (Pentax, Tokyo, Japan), Fuji Intelligent Chromo Endoscopy (FICE; Fujinon, Tokyo, Japan).\textsuperscript{41}

Confocal laser endomicroscopy is another advanced imaging technique that makes histologic assessment possible at the cellular and subcellular levels during endoscopy.\textsuperscript{42} The potential application of confocal laser endomicroscopy in IBD patients will be in combination with white-light endoscopy or chromoendoscopy.

Advanced endoscopic imaging modalities including high-definition endoscopy, chromoendoscopy, virtual chonendoendoscopy and confocal laser endomicroscopy have the potential to significantly improve the detection of flat and subtle dysplasia without the need for random biopsies. In addition, these novel techniques aid in decision-making and make it possible to resect a potentially dysplastic or neoplastic lesion at the time of CRC screening, even before having the results of biopsy.\textsuperscript{43}

**Conclusion:**

Endoscopy is fundamental to the care of patients with inflammatory bowel disease (IBD) and is essential for diagnosing and treating both Crohn’s disease (CD) and ulcerative colitis (UC). Endoscopy is used to make an initial diagnosis of IBD, distinguish CD from UC, assess disease extent and activity, monitor response to therapy, survey for dysplasia, and provide endoscopic treatment strictures. The new advances in endoscopy resulted in a major paradigm shift in how we diagnose and treat patients with IBD. Endoscopy as a historic diagnostic tool has been turned into an essential mean in surveillance and treatment of patients with IBD.

**References**


Inflammatory Bowel Disease


Uses of ENTYVIO® (vedolizumab):

ENTYVIO is a prescription medicine used in adults:

- with moderate to severe ulcerative colitis (UC) when certain other UC medicines have not worked well enough or cannot be tolerated. ENTYVIO may help to: begin reducing some symptoms, induce and maintain remission, reduce or stop the use of corticosteroids, and improve the way the lining of your large intestine looks to your healthcare provider.

- with moderate to severe Crohn’s disease (CD) when certain other CD medicines have not worked well enough or cannot be tolerated. ENTYVIO may help to: begin reducing some symptoms, achieve remission, and reduce or stop the use of corticosteroids.

Important Safety Information

- Do not receive ENTYVIO if you have had an allergic reaction to ENTYVIO or any of its ingredients.

Please see additional Important Safety Information on the next page.
Important Safety Information about ENTYVIO® (vedolizumab)

• Do not receive ENTYVIO if you have had an allergic reaction to ENTYVIO or any of its ingredients.
• ENTYVIO may cause serious side effects, including:
  Infusion and serious allergic reactions can happen while you are receiving ENTYVIO or several hours after treatment. You may need treatment if you have an allergic reaction. Tell your healthcare provider or get immediate medical help if you get any of these symptoms during or after an infusion of ENTYVIO: rash, itching, swelling of your lips, tongue, throat or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing).
  ENTYVIO may increase your risk of getting a serious infection. Before receiving and during treatment with ENTYVIO, tell your healthcare provider if you think you have an infection or symptoms of an infection, such as fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination.
  Although it has not been reported with ENTYVIO, it may be possible for a person to get progressive multifocal leukoencephalopathy (PML) (a rare, serious brain infection caused by a virus). People with weakened immune systems can get PML, which can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any of the following symptoms: confusion or problems thinking, loss of balance, change in the way you walk or talk, decreased strength or weakness on one side of the body, blurred vision, or loss of vision.
  Liver problems can happen in people who receive ENTYVIO. Tell your healthcare provider right away if you have any of the following symptoms: tiredness, loss of appetite, pain on the right side of your abdomen, dark urine, or yellowing of the skin and eyes (jaundice).
  The most common side effects of ENTYVIO include common cold, headache, joint pain, nausea, fever, infections of the nose and throat, tiredness, cough, bronchitis, flu, back pain, rash, itching, sinus infection, throat pain, and pain in extremities. These are not all the possible side effects of ENTYVIO. Call your healthcare provider for medical advice about side effects.
  Before receiving ENTYVIO, tell your healthcare provider about all of your medical conditions, including if you: have or think you may have an infection or have infections that keep coming back; have liver problems; have tuberculosis (TB) or have been in close contact with someone with TB; have recently received or are scheduled to receive a vaccine; or if you are pregnant, breastfeeding, plan to become pregnant, or plan to breastfeed.

Please see the Medication Guide for ENTYVIO on the adjacent page and talk with your healthcare provider.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

ENTYVIO is a trademark of Millennium Pharmaceuticals, Inc., registered with the U.S. Patent and Trademark Office, and is used under license by Takeda Pharmaceuticals America, Inc.

© 2015 Takeda Pharmaceuticals U.S.A., Inc. All rights reserved. Printed in U.S.A./September 2015 USD/VED/15/0198
Medication Guide
ENTYVIO (en ti' ve oh) (vedolizumab)

What is the most important information I should know about ENTYVIO?

ENTYVIO may cause serious side effects, including:

- **Infusion and serious allergic reactions.** These reactions can happen while you are receiving ENTYVIO or several hours after treatment. You may need treatment if you have an allergic reaction. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an infusion of ENTYVIO: rash, itching, swelling of your lips, tongue or throat, or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing).

- **Infections.** ENTYVIO may increase your risk of getting a serious infection. Before receiving ENTYVIO and during treatment with ENTYVIO, tell your healthcare provider if you think you have an infection or have symptoms of an infection such as fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination.

- **Progressive Multifocal Leukoencephalopathy (PML).** Although it has not been reported with ENTYVIO, it may be possible for a person to get progressive multifocal leukoencephalopathy (PML) (a rare, serious brain infection caused by a virus). People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any of the following symptoms: confusion or problems thinking, loss of balance, change in the way you walk or talk, decreased strength or weakness on one side of the body, blurred vision, or loss of vision.

- **Liver Problems.** Liver problems can happen in people who receive ENTYVIO. Tell your healthcare provider right away if you have any of the following symptoms: tiredness, loss of appetite, pain on the right side of your stomach (abdomen), dark urine, or yellowing of the skin and eyes (jaundice). See "What are the possible side effects of ENTYVIO?" for more information about side effects.

What is ENTYVIO?

ENTYVIO is a prescription medicine used in adults:

- with moderate to severe active ulcerative colitis (UC) when certain other UC medicines have not worked well enough or cannot be tolerated:
  - to begin helping some of your symptoms
  - in people who respond to ENTYVIO, to help get UC under control (induce remission) and keep UC under control (maintain remission)
  - for people who respond to ENTYVIO, you may be able to reduce or stop the use of corticosteroid medicines
  - to improve the way the lining of your large intestine looks to your healthcare provider during colonoscopy

- with moderate to severe active Crohn’s disease when certain other Crohn’s disease medicines have not worked well enough or cannot be tolerated:
  - to begin helping some of your symptoms
  - in people who respond to ENTYVIO, to help get Crohn’s disease under control (achieve remission)
  - for people who respond to ENTYVIO, you may be able to reduce or stop the use of corticosteroid medicines

It is not known if ENTYVIO is safe and effective in children under 18 years of age.

Who should not receive ENTYVIO?

Do not receive ENTYVIO if you have had an allergic reaction to ENTYVIO or any of the ingredients in ENTYVIO. See the end of this Medication Guide for a complete list of ingredients in ENTYVIO.

Before receiving ENTYVIO, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection, think you may have an infection or have infections that keep coming back (see “What is the most important information I should know about ENTYVIO?”).
- have liver problems
- have tuberculosis (TB) or have been in close contact with someone with TB.
- have recently received or are scheduled to receive a vaccine. Talk to your healthcare provider about bringing your vaccines up-to-date before starting treatment with ENTYVIO.
- are pregnant or plan to become pregnant. It is not known if ENTYVIO will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while receiving ENTYVIO.
- are breastfeeding or plan to breastfeed. It is not known if ENTYVIO passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you take or have recently taken Tysabri (natalizumab), a Tumor Necrosis Factor (TNF) blocker medicine, a medicine that weakens your immune system (immunosuppressant), or corticosteroid medicine.

How will I receive ENTYVIO?

- ENTYVIO is given through a needle placed in a vein (intravenous infusion) in your arm.
- ENTYVIO is given to you over a period of about 30 minutes.
- Your healthcare provider will monitor you during and after the ENTYVIO infusion for side effects to see if you have a reaction to the treatment.

What are the possible side effects of ENTYVIO?

ENTYVIO may cause serious side effects. See “What is the most important information I should know about ENTYVIO?”

The most common side effects of ENTYVIO include: common cold, headache, joint pain, nausea, fever, infections of the nose and throat, tiredness, cough, bronchitis, flu, back pain, rash, itching, sinus infection, throat pain, and pain in extremities.

These are not all of the possible side effects of ENTYVIO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about ENTYVIO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about ENTYVIO that is written for health professionals. Do not use ENTYVIO for a condition for which it was not prescribed.

What are the ingredients in ENTYVIO?

Active ingredient: vedolizumab
Inactive ingredients: L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose and polysorbate 80

Distributed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015
U.S. License No. 1898

For more information, go to www.ENTRYVIO.com or call 1-877-825-3327
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued: May 2014

ENTYVIO is a trademark of Millennium Pharmaceuticals Inc. and is used under license by Takeda Pharmaceuticals America, Inc.
All other trademark names are the property of their respective owners. ©2014 Takeda Pharmaceuticals America, Inc.

VMB245 R1_GFBS

L-BZV-0514-4
Out with the Old and In with the New?  
The Changing Approach to Colorectal Cancer Surveillance in Ulcerative Colitis

By Michael F. Picco, MD, PhD, FACG

Abstract: Colorectal cancer risk is high among patients with chronic long-standing extensive ulcerative colitis or colonic Crohn’s disease. The typical or conventional method of dysplasia detection is with white light colonoscopy. There have also been major advances in the field of image-enhanced colonoscopy with chromoendoscopy. Chromoendoscopy is a technique where either indigo carmine or methylene blue dye is sprayed on the colon during colonoscopy. This method has dramatically improved dysplasia detection. A recent international consensus conference called for the implementation of chromoendoscopy more broadly, especially for high-risk individuals. However, controversy exists as to the significance of dysplasia found with chromoendoscopy and which high risk patients are more likely to benefit from the technique.

Introduction

Ulcerative colitis (UC) and Crohn’s disease are chronic inflammatory bowel diseases. Ulcerative colitis only affects the colon, while Crohn’s disease may involve any portion of the tubular digestive tract. Significant colonic involvement by either of these diseases increases the risk of colorectal cancer (CRC). Unlike sporadic colon cancer, the classic adenoma cancer sequence does not occur in the development of colorectal cancer associated with UC. UC-related colorectal cancer (CRC) develops in a background of inflammation and regeneration. Unlike the adenoma precursor in sporadic CRC, the precancerous lesion in UC is cellular dysplasia arising from flat mucosa which may not be readily seen by standard white light colonoscopy.

Conclusions related to ulcerative colitis, also apply to colonic Crohn’s disease. With the advent of newer, more effective treatments for these diseases, surgery is becoming less common so that many patients with significant colonic involvement will delay, if not avoid, surgery. The risk of colorectal cancer in these patients increases with time so effective surveillance programs are essential. Recent advances in image enhancing colonoscopy have revolutionized the field.

What are the risks for colorectal cancer in chronic ulcerative colitis?

Early studies suggested that the risk of CRC in UC was about six times that of the general population. However, a more recent meta-analysis concluded that the risk is half as much. The reasons for this difference may be due to selection bias (i.e. referral based vs. community based populations), better medical therapies, and better methods of dysplasia detection. Understanding individual patient risk has shaped surveillance programs. The most important risk factors for CRC in UC are disease duration, anatomic extent of the disease, and presence of primary sclerosing cholangitis. (Table 1) Patients with additional risk factors of family history of CRC, presence of pseudopolyps, and greater severity of inflammation may also benefit from more intensive surveillance.

Table 1. Risk Factors for Colorectal Cancer in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Minor Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent Right sided colitis</td>
<td>Family History of Colorectal Cancer</td>
</tr>
<tr>
<td>Pancolitis&gt;&gt;Left sided colitis&gt;&gt;&gt;</td>
<td>Persistent Active Inflammation of the colon</td>
</tr>
<tr>
<td>proctitis/proctosigmoiditis = non-colitis population</td>
<td>Pseudopolyps (Inflammatory polyps)</td>
</tr>
</tbody>
</table>
Disease extent and duration

Ulcerative colitis is classified based on anatomic extent for medical therapy and CRC surveillance. Proctitis or proctosigmoiditis refers to any inflammation from the anus up 30 cm; left-sided colitis extending above 30 cm with any involvement up to the splenic flexure; and any disease extending proximal to the splenic flexure is called extensive or pancolitis. For disease initially confined to the lower colon there is a significant risk that it may spread more proximally. The progression of proctosigmoiditis to left-sided colitis was estimated at 50 percent and for left-sided to pancolitis 70 percent at 25 years. These findings impact the approach to surveillance.

The risk of CRC for proctitis is thought to be no higher than a non-colitis population, whereas risk for left sided colitis and pancolitis is threefold and six to fifteen-fold that of the general population respectively. Since Crohn's disease can involve any part of the colon, significant extent is loosely defined as at least one-third of the colon involved with rates of CRC similar to UC based on extent. Furthermore, extent is based on microscopic involvement so that biopsy is needed.

The risk of CRC in UC has been estimated at two percent at 10 years, eight percent at 20 years and 18 percent at 30 years duration. These findings have shaped current surveillance guidelines. While more recent studies have suggested that the rates may actually be lower, they are increased and vary based on the population studied.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the bile ducts. It is strongly associated with colonic IBD with at least 75 percent of PSC patients having chronic colitis. Chronic colitis in PSC tends to be a milder, often subclinical, disease but with a fourfold increase in CRC risk compared to UC alone. Given this strong association and high cancer risk, all patients with PSC should undergo colonoscopy with random biopsy. If chronic colitis is found, surveillance colonoscopy begins at diagnosis.

Minor Risk Factors

While not considered in existing surveillance guidelines, family history of CRC, disease activity, and pseudopolyps (benign inflammatory polyps) also increase the risk of CRC in UC. Family history of sporadic (non-colitis associated) CRC increases the risk twofold. While age at diagnosis may increase the risk, results are inconsistent. Disease activity as measured by histological inflammation has been associated with a three to fourfold increased risk, emphasizing that disease activity be defined based on microscopic involvement. The detection of flat dysplastic lesions can be challenging when there is quiescent colitis and active disease present. Similarly, the presence of pseudopolyps also leads to higher risk because true dysplasia is more difficult to see and these benign polyps are a marker for previous severe inflammation.

Current surveillance guidelines

The goal of surveillance colonoscopy in chronic UC is the detection of dysplasia. Dysplasia detection with standard white light colonoscopy relies on identifying and removing lesions at colonoscopy and obtaining 33 random biopsies throughout the colon. This is based on the argument that certain dysplasia is “invisible.” It has been estimated that 33 biopsies achieve a 90 percent positive predictive value for dysplasia. However, yields on random biopsy are very low and can range from 0.1 to 0.2 percent or one per thousand to one per 500 random biopsy samples.

Surveillance guidelines start with the recommendation that all patients with UC should undergo screening colonoscopy with extensive biopsies after eight years of symptoms to determine disease extent. These guidelines also require a patient to have an adequate colon preparation and to be in endoscopic remission to maximize dysplasia detection. Patients with pan-colitis or left sided colitis should begin surveillance within one to two years later. This also applies to Crohn's colitis where at least one-third of the colon is involved. Patient with PSC and colitis begin surveillance immediately at diagnosis. Surveillance continues every one to two years.

The significance of dysplasia

Dysplasia is defined as low-grade or high-grade based on histological appearance and on expert pathologist interpretation, confirmed by a second pathologist. The degree of dysplasia has been shown to predict the likelihood of CRC at colectomy. Nearly 20 percent of patients who had colectomy for low-grade dysplasia and 42 percent for high grade had CRC in the colectomy specimen. Where a visible lesion, termed a dysplasia associated lesion or mass (DALM), is found, 43 percent had CRC in the colectomy specimen. When the pathologist was unsure if dysplasia was present, one-third progressed to high-grade dysplasia or cancer. These sobering findings, in part, led to the aggressive recommendation for colectomy for DALM lesions, high-grade dysplasia and low-grade dysplasia.
The recommendation of colectomy for high-grade and low-grade dysplasia implies dysplasia may be endoscopically invisible. There is broad acceptance that “invisible” high-grade dysplasia is an indication for colectomy. For low-grade dysplasia, recommendations are more controversial. If low-grade dysplasia is found in one area on initial colonoscopy, closer surveillance colonoscopy is acceptable. If it is found in more than one area or on subsequent colonoscopies, colectomy is generally recommended.5

The most controversial area in dysplasia detection is in the definition of a dysplasia associated lesion or mass (DALM). The controversy rests in whether a true UC-related dysplastic lesion can be distinguished from a sporadic (non-colitis associated) adenoma. The potential consequences of failure to distinguish are extreme, ranging from an unnecessary colectomy to a missed opportunity to cure CRC. Two studies have found that it is safe to simply remove lesions that are sporadic “adenoma like.” In a study of 48 UC patients with an average duration of 25 years, 70 polyps were removed and no cancers developed after 4.1 years of follow-up.16 Similarly, in a surveillance group with a UC duration averaging 10 years, no cancers developed after 42 months with one case of low-grade dysplasia.17 The decision to remove or refer for colectomy is based on endoscopic appearance and patient characteristics. Lesions that are outside an area of colitis, pedunculated or discrete (clear borders) can safely be removed. Biopsies should be taken from around the lesion and if dysplasia is found the patient should be referred to a specialized center for consideration of colectomy. Older patients are more likely to have sporadic adenomas, while patients with PSC are more likely to have UC related dysplasia.

Does Colorectal Cancer Surveillance Prolong Survival?

A Cochrane analysis published in 2008 found no conclusive benefit of UC surveillance for CRC survival.18 Evidence was indirect with, at best, trends toward improved survival that did not reach statistical significance. There was an apparent benefit in that CRC diagnosed with surveillance tended to be at an earlier stage resulting in better survival. However, as the authors point out, this may simply be due to lead-time bias where survival appears to be prolonged only because the cancers were diagnosed earlier. The authors did conclude that “lower quality evidence, however supports the continued use of some form of surveillance for these patients.” This analysis was based largely on studies that used standard definition rather than high definition colonoscopy and did not utilize advanced imaging techniques.

Figure 1. Chromoendoscopy improves dysplasia detection and lesion resolution. A colonic dysplastic lesion seen with high definition white light (A) and then with chromoendoscopy (B) is shown.

Advanced Endoscopy Imaging: Chromoendoscopy and The New Era of Surveillance

Current surveillance methods predominantly rely on a cumbersome, time-consuming and expensive process of multiple randomly obtained (non-targeted) mucosal biopsies to detect dysplasia. Standard colonoscopy alone is imperfect, lacking acceptable sensitivity and specificity.19,20 Chromoendoscopy (CE) involves the spray application of dye solutions, typically indigo carmine or methylene blue, to the colonic mucosa.21

Prior to chromoendoscopy, the colon is washed with water on insertion of the scope to clear any debris and to provide an adequate colonic preparation. Either dye is then mixed in water at concentrations ranging from one to two percent and sprayed on the colon on withdrawal from the cecum (Figure 1). Obtaining biopsies of visible lesions with either dye improves dysplasia detection. Methylene blue staining differentiates non-neoplastic and neoplastic lesions with a sensitivity of 93 percent and specificity of 93 percent.22 Dysplasia detection rates are up to fourfold higher with CE.23,24

Despite convincing data from several well-designed studies, CE has not been universally accepted. It has been recommended by the Crohn’s and Colitis Foundation of America and the American Gastroenterological Association,12,25 but not by the American College of Gastroenterology (ACG).26 The ACG chose not to advocate routine use of this technique because of lack of knowledge of the natural history of lesions seen only under CE. The ACG has suggested that CE may have benefit for “high risk” patients. To understand whether removal of small lesions seen with CE decreases the risk of subsequent colon cancer would require a large natural history study that is unlikely to be performed in the near future.
Difficulties with adopting CE into clinical practice include lack of endoscopist experience, reliability of image interpretation, and the additional time needed to perform the procedure. These issues were addressed in a study that looked at the implementation of a chromoendoscopy surveillance program for UC. Six endoscopists without experience in chromoendoscopy had similar rates of dysplasia detection compared to “experts” in the field after only 15 chromoendoscopy cases were completed.

UC surveillance CE is recommended for those with expertise in the technique, but the dye-spraying process only 15 chromoendoscopy cases were completed.

UC surveillance CE is recommended for those with expertise in the technique, but the dye-spraying process only 15 chromoendoscopy cases were completed. However, surveillance with random biopsies, as is the standard of care, results in very low dysplasia detection rates and is generally reimbursed at the same rate as colonoscopy with biopsy. If this technique were abandoned in favor of directed CE biopsies, overall procedure time is likely to be affected very little and cost savings realized by restricting biopsies to targeted lesions. Unfortunately, narrow band imaging, a convenient technology installed in many colonoscopies, has not been shown to increase dysplasia detection in UC.

The New Era: SCENIC Guidelines

In an effort to provide, in the era of high definition colonoscopy and chromoendoscopy, updated guidelines for adoption into surveillance colonoscopy for chronic ulcerative colitis, an international multidisciplinary group was convened that consisted of inflammatory bowel disease specialists and interventional endoscopists. The Surveillance for Colorectal Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Guidelines (SCENIC) provides new recommendations for the application of standard colonoscopy and chromoendoscopy to surveillance and better classification of lesions found.

High definition colonoscopies are recommended for surveillance. Chromoendoscopy is recommended if standard definition and suggested if high definition scopes are used. The panel could not reach a consensus on random biopsies. Currently, biopsies can be done with standard colonoscopy and with chromoendoscopy.

The SCENIC guidelines emphasized whether a lesion seen at colonoscopy is polyoid or non-polyoid (little or no protrusion above the mucosa) endoscopically resectable or unresectable. The terms of “dysplasia associated lesion or mass (DALM)” and “adenoma like lesion (ALM)” were abandoned. Resectable lesions were defined as having distinct margins that can be completely removed by endoscopy and with biopsies of the surrounding tissue without dysplasia.

The authors recommended that such lesions do not require colectomy but can be followed with closer surveillance (i.e. every six months). While endoscopic removal of polyoid lesions is generally accepted, the additional recommendation that non-polyoid (flat) dysplasia be resected and safely followed by surveillance, rather than colectomy, is controversial. SCENIC did set up a framework for further investigation that is needed to advance the field. Despite these consensus group recommendations, chromoendoscopy has failed to be endorsed for all surveillance procedures. Some academic centers have adopted it for high-risk patients with a history dysplasia, colon polyps or pseudopolyps, PSC and others on a case by case basis.

Conclusion

Long-standing extensive ulcerative colitis increases the risk of CRC. Available methods of surveillance with conventional colonoscopy result in low rates of dysplasia detection. Chromoendoscopy has ushered in a new era of improved dysplasia detection among individuals with ulcerative colitis at risk for colorectal cancer. The technique is simple, easy to learn and leads to improved dysplasia detection. However, many questions remain to be answered including whether all UC patients at risk for CRC should have chromoendoscopy, the natural history of the lesions that are found, and whether the technique leads to lower rates of CRC. For now, for endoscopists with experience in chromoendoscopy, it is reasonable to at least apply the technique to high risk patients such as those with prior dysplasia, polyps and/or PSC.

References

Inflammatory Bowel Disease


Vaccination Recommendations for Patients with Inflammatory Bowel Disease

By Anhtung Chau, MD

Abstract: Inflammatory bowel disease (IBD) is a disorder involving the GI tract with poorly understood pathogenesis. Medical treatment for IBD has been evolving rapidly, but mostly comprises of immunosuppression similar to transplant-type medications. Immunization is safe and potentially life-saving, if done appropriately. It is important for clinicians to know the schedule and recommendations in order to vaccinate patients with IBD early if anticipating escalation of immunosuppressive therapy.

Introduction

Inflammatory bowel disease (IBD) is a disorder involving the GI tract and it typically comprises of two major disorders: Crohn’s disease (CD) and ulcerative colitis (UC). The pathogenesis for these disorders is poorly understood despite the distinct characteristics. Crohn’s disease involves the entire GI tract from mouth to perianal area and is characterized by transmural inflammation with strictures and fistulization. Ulcerative colitis involves the rectum and extends into proximal colon in a continuous fashion. In 2007, the prevalence for CD was 201 per 100,000 and the prevalence for UC was 238 per 100,000.1

Medical treatment for Inflammatory Bowel Disease has been evolving rapidly and primarily takes the form of immunosuppression. The treatment ranges from mild topical treatment, such as mesalamine and budesonide, to systemic steroids (prednisone). For more severe cases, as well as for steroid sparing treatment, physicians have been using immunomodulators (azathioprine and methotrexate), as well as biologic agents (infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab). Also, in selected cases, transplant-type immunosuppression such as tacrolimus, cyclosporine and mycophenolate are used in treatment of IBD.

Immunization in IBD patients:

Immunization has been well recognized in the world of solid organ and hematopoietic transplant, cancer patients receiving chemotherapy and patients with HIV/AIDS. In 2013, international infectious disease specialists prepared an updated guideline for vaccination of immunocompromised adults and children.2 However, physicians are not doing too well in terms of immunization of patients with IBD. In 2008, a study looked at 116 IBD patients versus 100 control patients. The rate of screening for immunization was lower in IBD patients (75 percent vs 84 percent).3 Prior to this, there was a study in 2006 that surveyed 169 IBD patients, with 145 patients reported being on current or previous history of immunosuppression.4 In this group, only 28 percent recalled having annual influenza vaccine, 9 percent recalled having pneumococcal vaccine and 45 percent recalled having tetanus vaccine in the past 10 years. In addition, only 31 percent of the 75 patients who were identified at risk for hepatitis B were vaccinated against hepatitis B.4

Physicians also must decide which patients require vaccination. In 2011, Wasan’s group randomly sent out survey to 1,000 members of American College of Gastroenterology (ACG) regarding vaccination in IBD patients.5 Only 108 members (11 percent) returned the survey and only half of the gastroenterologists reported asking about immunization history routinely. Seven percent reported that they never ask their IBD patients about their immunizations.5 Of these returned surveys, 64 percent of the gastroenterologists thought that the primary care providers should be determining which vaccines to give and 83 percent thought primary care providers should be giving the vaccines to the IBD patients.

Definition of immunocompromised hosts:

There is a consensus by experts in term of who is defined as immunosuppressed in the IBD population. IBD patients who are considered to be immunosuppressed are patients using corticosteroid at ≥20 mg/day for more than two weeks or within three months of stopping; patients on azathioprine or 6-mercaptopurine or who have recently discontinued within three months; patients on methotrexate or who
have recently discontinued within three months; patients on biologic agents; or patients with severe protein-calorie malnutrition.\textsuperscript{6}

**Vaccination schedule:**

The timing of vaccination is also quite essential. Live-attenuated vaccines cannot be given to immunosuppressed patients. This means it is imperative that physicians anticipate and vaccinate the patients before they become immunocompromised. Live-attenuated vaccines include MMR (measles, mumps, rubella), varicella, herpes zoster, rotavirus, yellow fever, oral typhoid and polio, and intranasal influenza.\textsuperscript{7,8} MMR is routinely given to all children starting at age one in two doses. In adults with unknown status, titers can be checked and the vaccine can be given if there is no plan for immunosuppression within six weeks.\textsuperscript{2,7,8} Varicella is recommended for all immunocompetent children and adults if there is no known history of exposure. Disseminated varicella occurs in 20/100,000 adults and has a mortality rate of about 30 percent.\textsuperscript{4} It is typically recommended by experts to avoid immunosuppression for one to three months after vaccination. Zoster vaccine has the same strain as varicella, except it is 14 times more potent.\textsuperscript{9} It is recommended for persons who are 60 years or older and patients should avoid immunosuppression for four weeks after immunization.\textsuperscript{2} Rotavirus is administered at age 2 and 4 months and the maximum age for the first dose in the series is 14 weeks. However, infants born to mothers on infliximab, which can cross placenta, can be immunosuppressed for up to six months. Rotavirus vaccine is typically avoided in these cases.\textsuperscript{7,8}

Inactivated vaccines should be given to all IBD patients, regardless of immunosuppressed state. These include influenza, tetanus, HPV, pneumococcal, meningococcal, hepatitis A and hepatitis B. For influenza vaccine, the intramuscular form should be given annually and the intranasal form should be avoided.\textsuperscript{2,7,8} Tetanus should be given to all patients in a 3-dose series, followed by a booster every 10 years.\textsuperscript{2} The HPV vaccine is a quadrivalent vaccine that targets the four HPV serotypes (6, 11, 16 and 18). It is indicated for women and men age 11 to 26.\textsuperscript{7,8} It has been shown that patients with IBD have higher incidence of abnormal Pap smears (47 percent vs. control) and are more likely to have higher-grade lesions.\textsuperscript{10} Pneumococcal vaccine is a 23-valent pneumococcal polysaccharide vaccine that is recommended for all IBD patients, regardless of age or immunosuppressive status. A one-time dose revaccination is recommended after five years in patients older than 65 or who are immunosuppressed.\textsuperscript{2,7,8} Meningococcal vaccine is recommended to all at-risk patients who have not been vaccinated. This includes patients who are asplenic, patients with complement deficiencies, college students who live in dormitories, or military recruits.\textsuperscript{7,8} For hepatitis B, it is routinely recommended to check for serology before initiating biologic agents. If the patient is not immune, the vaccine series should start at month 0, 2 and 6.\textsuperscript{8}

**Adequacy of immunogenicity:**

One important question to ask is the adequacy of immunogenicity of patients with IBD and the effectiveness of vaccination. In patients with IBD, the levels of serum immunoglobulins are normal and also slightly higher than normal circulating antibodies. These patients also have enhanced T-cell responses to luminal antigens. These factors suggest an IBD patient should have an appropriate response to vaccination.\textsuperscript{6} However, in clinical practice there is limited data in patients with IBD. It was shown that when patients were on monotherapy with either azathioprine or 6-MP, their responses were comparable to control subjects when given influenza vaccine after at least 24 weeks of therapy.\textsuperscript{11} However, it was also shown that there was inadequate response to influenza vaccine in patients who were on infliximab and azathioprine.\textsuperscript{12} Therefore, larger studies are needed to evaluate for sustainability of immune response and timing for booster dose.

**Conclusion:**

It is important for clinicians to vaccinate patients with IBD early if anticipating escalation of immunosuppressive therapy. Vaccination is safe, and potentially lifesaving, if done appropriately. It is recommended to check titers for hepatitis A and B, varicella and MMR during the initial visit prior to vaccination. All patients should receive inactive vaccine for Tdap, HPV, influenza, pneumococcus, meningococcus and hepatitis A and B, regardless of immunosuppressive status. The live-attenuated vaccines such as MMR, varicella and zoster should only be administered if there is no plan for immunosuppression in the next 4-12 weeks.\textsuperscript{6}
References


The Extraintestinal Manifestations of Inflammatory Bowel Disease

By John M. Petersen, DO, FACG, FACP

Abstract: Inflammatory bowel disease (IBD) is associated with a variety of extraintestinal manifestations that may produce more morbidity than the underlying intestinal disease, and pre or post date the presentation or activity of IBD. Nearly 40 percent of patients with IBD will have at least one of these features. Some are related to the underlying inflammation (joint, skin, ocular, oral). Others are seen in small bowel dysfunction (gallstones, kidney stones, obstructive uropathy). Osteoporosis, anemia, hepatobiliary disease, fatulosis, amyloidosis, and neuropathy may be seen. A number of pathogenic mechanisms play a role in their development. Early recognition is paramount to avoid potential morbidity and mortality.

Introduction

The inflammatory bowel diseases (IBD), notably Crohn's disease (CD) and ulcerative colitis (UC) are chronic, debilitating, systemic inflammatory diseases that may involve the entire gastrointestinal tract. Between 30 and 40 percent of patients with IBD develop extraintestinal inflammation and clinically significant disorders termed extraintestinal manifestations (EIM). The most common EIMs affect the joints, skin, eyes, and biliary tract. Many times, the EIMs associated with these inflammatory diseases bear a very negative impact on the overall course of the disease. Therefore, it is very important to identify the particular extraintestinal disorder and treat it accordingly, as well as treat the underlying inflammatory bowel disease. At times, certain EIMs such as axial arthritis, pyoderma gangrenosum, uveitis, and primary sclerosing cholangitis run a very independent clinical course. With the advent of the biologic response modifiers such as the anti-TNF inhibitors, we have seen marked improvement in these extraintestinal manifestations.

Extraintestinal IBD-related immune diseases can be classified into two major groups: The first includes reactive manifestations associated with intestinal inflammatory activity and therefore reflect a pathogenic mechanism common with the intestinal disease. These include arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, and the ocular findings of iritis and uveitis. The second category includes autoimmune diseases that appear to be independent of the underlying bowel disease and may reflect only a susceptibility to autoimmunity. These disorders are not considered as specific features but as autoimmune associated diseases and include ankylosing spondylitis, primary sclerosing cholangitis, primary biliary cirrhosis, alopecia areata, and thyroid autoimmune disease.1

Pathogenesis of Immune Related Extraintestinal Manifestations in IBD

Evidence from many studies in genetically susceptible animal models of colitis suggest a crucial role of enteric flora in activating the immune system against bacterial antigens and against portions of the colonic mucosa on the basis of an antigenic cross reactivity.2 The sharing of these colonic antigens by extraintestinal organs, associated with a genetic susceptibility, would eventually lead to an immune attack on these organs. One prime example is seen in primary sclerosing cholangitis, most commonly associated with ulcerative colitis. In that disorder, the presence of anticolon mucosal autoantibodies cross react with biliary epithelium. In addition, a colonic epithelial protein and the human tropomyosin isoform 5, which are not only expressed in the colon but also in the biliary tract, skin, eyes, joints, have been suspected to be the major common targets of autoimmune attack in the extraintestinal organs of IBD patients. It is unclear why the extraintestinal organs are not always involved at the same time and why these autoantibodies are absent in colonic Crohn's disease. A partial explanation is that the genetic factors or local co-existent damage factors, such as infection and trauma, could regulate the display of these cryptic antigens and the susceptibility to autoimmune attack.

As part of inflammatory bowel disease in general, a physician can identify an immune induction site where T cells are primed, represented by the colon and the effector sites that are the extraintestinal organs. Immune cells infiltrate the effector sites with the help of adhesion molecules such as alpha-4 B7 integrin and vascular adhesion protein that have a cytokine-mediated overexpression.
Inflammatory Bowel Disease

In certain tissues. Autoimmune attack can happen many years after the removal of the colon.³

In the case of primary sclerosing cholangitis, it is suspected that memory lymphocytes that have been primed in the bowel can recirculate for many years after the removal of the colon. This can cause damage until the occurrence of a stimulus in the liver that activates inflammation and overexpression of the adhesion molecules and persistent lymphocyte recruitment. Interference with adhesion molecules may be very useful in the treatment of extraintestinal manifestations of IBD.

The high prevalence of p-ANCA in patients with UC, commonly associated with PSC, Erythema nodosum (EN) and uveitis, supports the role of autoimmune mechanisms in the development of EIM. (Table 1)

There appears to be great genetic susceptibility with EIMs in inflammatory bowel disease. These EIMs have a familial predisposition seen in 83 percent of concordance among siblings, and there appears to be a strong genetic influence leading to the identification of many suspected predisposal type genes.³ The Human Leukocyte Antigen (HLA) system is considered one of the major genetic markers associated with EIMs in IBD. It has been very clearly reported that UC patients that have HLA-B8 or the DR3 phenotype have a tenfold higher risk of primary sclerosing cholangitis.⁴ We see a variety of other HLA phenotypes that predispose people to ocular and articular manifestations, especially patients with the HLA-B27 and B58 phenotypes who also have a higher risk of uveitis. HLA-B27 is strongly associated (up to 80 percent) with ankylosing spondylitis.² Polymorphisms of alpha-TNF have been associated with erythema nodosum in IBD patients. Polymorphisms of NOD2 (Card15) are associated with familial Crohn’s, ileal disease, fibrostenotic Crohn’s, and sacroiliitis.²

<table>
<thead>
<tr>
<th>Table 1. Pathogenesis of EIM in IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Genetic susceptibility</td>
</tr>
<tr>
<td>- Antigenic display of autoantigen</td>
</tr>
<tr>
<td>- Aberrant self-recognition</td>
</tr>
<tr>
<td>- Immunopathogenetic autoantibodies (anti-tropomysin)</td>
</tr>
<tr>
<td>- Immune complex formation</td>
</tr>
<tr>
<td>- Cytokine imbalances</td>
</tr>
<tr>
<td>- Bacterial antigens or toxins</td>
</tr>
</tbody>
</table>

In the past decade, we have seen the concept of dysbiosis of the gut microbiome emerge as a potential pathogenetic focus in IBD. The judicious use of antibiotics, probiotics, prebiotics, enteral nutrition, and fecal transplantation are flourishing.

Arthropathies

The reported incidence of arthropathies associated with IBD range from 4 to 23 percent.³ Two types have been defined and the distinction is supported by differences in genetic susceptibility. Type 1 is a large joint pauciarticular arthropathy that occurs at times of IBD activity. Type 2 is polyarticular small joint (frequently 5 or more joints) arthropathy where activity is largely independent of IBD activity. Axial arthritis includes sacroiliitis and ankylosing spondylitis which have characteristic radiologic changes. (Figure 1) HLA B-27 is overrepresented in axial arthritis related to IBD.

Figure 1: Sacroiliitis in Crohn’s disease

Type 1 arthropathy affects the weight-bearing joints including the ankles, knees, hips, wrists, elbows, and shoulders. Pauciarticular refers to fewer than 5 joints being affected. The arthritis is usually acute and self-limiting, and usually resolves within a few weeks as the disease itself decreases. It typically does not leave permanent joint damage. These joints are painful, tender, and swollen. The differential diagnosis could include osteoarthritis, septic arthritis, pseudogout, and, occasionally, rheumatoid arthritis.

The polyarticular peripheral arthropathy, or type 2, affects the small joints of the hands as a symmetrical...
Inflammatory Bowel Disease

Inflammatory Bowel Disease treatment of the underlying active disease. Treatment options include the cautious use of steroids, immunomodulation drugs, and anti-TNF therapy. Sulfasalazine, a drug initially designed to be used for rheumatoid arthritis, can at times be very helpful, but evidence to support its long-term use is lacking. There is concern that some of the nonsteroidal anti-inflammatories may aggravate underlying colitis; however, caution can be used in some cases of colitis exacerbations. Methotrexate and Imuran can be of great benefit in both the axial and spondyloarthropathies. The safety and efficacy of infliximab and Adalimumab in ankylosing spondylitis associated with IBD is very well established.6

Cutaneous Manifestations

The incidence of various cutaneous problems associated with IBD can range anywhere from 2 to 35 percent.7 Erythema nodosum is quite easily recognized. These are raised, tender, red or violaceous subcutaneous nodules ranging from 1 cm to 5 cm in diameter. It usually affects the extensor surfaces of the extremities, especially in the lower legs, and commonly occurs at times of activity of the underlying IBD. Biopsy is usually not needed. EN seems to be more common in females, especially those with CD. Treatment is based on that of the underlying colitis or enteritis. Systemic steroids may be required. Immunomodulation with either azathioprine or 6-MP coupled with infliximab can be extremely helpful.

Ankylosing spondylitis presents with lower back pain beginning before the age of 30. There may be lumbar lordosis and limited spinal flexion. Spinal CT scans and bone scans are much more sensitive than plain radiographs, but the gold standard in diagnosis currently is magnetic resonance imaging.5 In advanced cases, the vertebral bodies may become squared with bony proliferation creating the typical and classic "bamboo spine." (Figure 2) HLAB-27 is found in close to 75 percent of patients with axial arthritis, but is less common than in patients with ankylosing spondylitis not associated with IBD. CD patients are affected more commonly by axial arthropathy than those with UC. The prevalence of AS in CD is 10 percent.5 Up to 70 percent of AS victims will have microscopic gut inflammation at Ileo-colonoscopy biopsies.5

The treatment of these arthropathies may include simple analgesics, nonsteroidal anti-inflammatories, mesalamine products, local steroid injections, and physical therapy. With type 1 peripheral arthritis, the emphasis should be on the treatment of the underlying active disease. In the management of IBD patients with arthritis, infliximab and Adalimumab are very efficacious in their treatment and prevention of acute exacerbations. They are also helpful in the management of the chronic disease state.8 Pyoderma gangrenosum (PG) (Figure 3) is a serious inflammatory dermopathy characterized by progressive painful, noninfectious skin ulcerations. At least half of pyoderma cases are associated with underlying inflammatory bowel disease. It
may also be seen in rheumatoid arthritis and certain hematologic malignancies. It appears that immunological factors and neutrophil dysfunction may play a role in its evolution. Classic pyoderma begins as a pustule or vesicle but then ruptures, becomes necrotic, and progresses to ulceration in several days. The lesion is extremely painful. These lesions tend to have a predilection for the lower extremities, but may occur adjacent to stomas or even on the genitalia. The patient may be systemically ill with fever, malaise, arthralgias, and myalgias. These ulcerations are infiltrated by inflammatory cells which are mostly neutrophils. The differential with PG includes infections, malignancies, vasculitides, venous stasis ulceration, and peripheral vascular disease. Skin biopsy may be helpful in excluding other conditions if inflammatory bowel disease is not lurking.

Without treatment, PG can last for years. Systemic steroids are first line therapy for PG and usually create a rapid response. On occasion, certain immune modulating treatment such as Dapsone, cyclosporin, mycophenolate, topical tacrolimus, or even intravenous immunoglobulins may be needed. Infliximab and adalimumab are clearly first line therapies. At times, aggressive debridement by a skilled surgeon with grafting may be needed. Hyperbaric oxygen may be of benefit. Antibiotics play no specific role in treating these lesions unless secondarily infected. Plasmapheresis has been employed for refractory PG. Overall, the treatment of the underlying inflammatory bowel disease allows these lesions to slowly heal. An atrophic scar may be left, and it is not unusual for it to take weeks or months to clear. Sweet’s syndrome is characterized by tender, red, inflammatory nodules or papules that usually affect the upper limbs, face, or neck. It is in the group of acute neutrophilic dermatopathies similar to pyoderma gangrenosum. This lesion has a strong predilection for women and mostly is seen in patients with colonic disease. As a rule, the rash is associated with active IBD disease, but may also precede the onset of intestinal symptoms and up to 21 percent of patients with eventual inflammatory bowel disease.

Ocular Manifestations

A wide range of ocular manifestations have been recorded in patients with IBD. These complications are commonly associated with joint complaints as well. The incidence varies from 4-12 percent in both UC and CD, although uveitis and iritis are more commonly seen in patients with UC, and episcleritis more commonly in Crohn’s disease.

Episcleritis is a painless red eye characterized by hyperemia of the sclera and conjunctiva with itching and burning. As a rule, this disorder does not require a specific treatment other than the underlying disease activity that is treated. It will respond to topical steroids.

Hepatobiliary Disease

It is estimated that 5-15 percent of patients with inflammatory bowel disease will develop some form of hepatobiliary disease. Now, with sophisticated magnetic resonance cholangiopancreatography (MRCP), that prevalence may be understated. Primary sclerosing cholangitis (PSC) constitutes the most important condition relatively specific to the underlying IBD. This disease has an unknown etiology, has no proven effective treatment, and liver transplantation is the only way of extending a patients’ life expectancy. Patients can also develop pericholangitis, steatosis, a nonspecific chronic hepatitis, cryptogenic cirrhosis, and cholelithiasis. PSC is a chronic cholestatic disease characterized by progressive inflammation of the intrahepatic and extrahepatic bile ducts followed by fibrosis and, in its worst case, biliary cirrhosis with liver failure. 70 percent of victims are male, most are HLA-DR3, B8 positive, and up to 75 percent of them will have IBD. Cholangiocarcinoma may also develop within this spectrum.
PSC can precede the initial diagnosis of IBD. In addition, some patients are diagnosed with PSC several years after having proctocolectomy. Therefore, patients with PSC should always undergo a colonoscopy to evaluate for inflammatory bowel disease. Typically what is seen is involvement of the colon with rectal sparing. At times, there may be some ileitis as well. These patients present with fatigue and abdominal pain, weight loss, pruritus, and then intermittent bouts of jaundice. Abnormal liver function tests include markedly elevated alkaline phosphatase and gamma-glutamyl transeptidase (GGTP). Bilirubin levels may slowly rise from 2 to 20. There may be a number of autoantibodies detected including ANA, anti-smooth muscle antibodies, and anti p-ANCA in close to 80 percent of patients. MRCP or endoscopic retrograde cholangiopancreatography (ERCP) can be diagnostic. Typically ERCP is reserved for patients that are thought to have a dominant stricture that can be investigated, brushed for malignant cytology, dilated, or even transiently stented for decompressive relief. (Figure 5) Patients with small duct PSC may need a liver biopsy to be confirmatory. Total colectomy does not seem to make a difference as to the clinical course of PSC. For patients with significant cholestasis, if an ultrasound is normal, and there do not appear to be any major drugs to incriminate, and if serological tests for other primary liver diseases are negative, then the probability of PSC increases. If MRCP is normal and PSC is still suspected, a liver biopsy may be very appropriate and safe to perform, rather than ERCP with its remote risk of pancreatitis. PSC substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma. Annual colonoscopy is recommended once the diagnosis of PSC is confirmed. The severity of UC is not related to the severity of the PSC.

**Figure 5:** PSC in chronic UC – Endoscopic retrograde cholangiopancreatography (ERCP) Image

PSC appears to respond to ursodeoxycholic acid, which improves abnormal liver function tests in cholestasis, but does not affect the overall course of the disease. A dose of 20 mg/kg may improve prognosis. It is possible that it also reduces the risk of colonic cancer in these patients. However, there is no firm evidence that ursodiol has a convincing effect on the course of this disease. In addition, a study on the long-term use of high dose ursodeoxycholic acid revealed an increased risk of colonic neoplasia in patients with UC and PSC. Therefore, the use of ursodiol for the management of PSC is currently not recommended in general.

Dilation of dominant strictures at the time of ERCP may improve cholestatic symptoms. On rare occasion, the placement of stents, preferably fully covered expandable metal stents, may be of benefit. Most of all, the goal is to avoid colonization of the biliary tree from duodenal contents as much as possible. Orthotopic liver transplantation is the therapy of choice for patients with end stage PSC and carries a fairly favorable five year survival rate of 80 percent. However, the risk of developing cholangiocarcinoma in these patients is paramount and is on the mind of every endoscopist involved with this disorder.

Autoimmune hepatitis, with or without overlap with PSC, is more common in patients with UC than CD. A granulomatous hepatitis is a rare manifestation of patients with Crohn’s. Cholelithiasis occurs in up to 30 percent of patients with IBD, especially in those with ileal Crohn’s or after an ileal resection. This is explained by the increased enterohepatic circulation of bilirubin and augmented re-absorption of bilirubin, caused by increased colonic bile salts in these patients. The increased risk of developing cholesterol gallstones might be caused by abnormal bile salt absorption and cholesterol supersaturated bile. In addition, reduced gallbladder motility in patients with IBD who have periods of fasting or may require total parenteral nutrition also seems to promote the development of cholelithiasis in these sick patients. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH) are often diagnosed in patients with IBD at a prevalence of close to 10 percent of patients with IBD, especially in those with UC and up to 20 percent in those with Crohn’s. Corticosteroids, methotrexate, Imuran and Total Parenteral Nutrition (TPN) may all promote the development of fatty liver disease in these patients. Patients with IBD have an increased risk of developing a severe complication of non-Hodgkin’s lymphoma. Several cases of hepatosplenic T cell lymphoma have been reported in patients with IBD, mostly in those who have been treated with a combination of anti-TNF therapy, the thiopurines, and corticosteroids. In view of the fatal course of this complication, the long-term use of a combination of these drugs should be used with extreme caution. Finally, PBC, chronic hepatitis, and portal vein thrombosis may be seen with greater prevalence in patients with IBD.

Pancreatic manifestations in IBD can include acute pancreatitis which may be precipitated by some of the drugs...
being used to treat the underlying condition. These include azathioprine, 5-ASA, Flagyl, and, occasionally, corticosteroids. Drug-induced pancreatitis typically resolves rapidly after discontinuation of the drug. Autoantibodies directed against pancreatic tissue have been described. There is a suggestion that inflammation of the duodenum and papilla in CD may account for some drainage difficulties and pancreatitis in these patients as well.

**Thromboembolic Events**

Venous and arterial thromboembolisms are disease specific extraintestinal symptoms in patients with IBD that can cause significant morbidity and mortality. It is thought that there is a two to fourfold increase of venous thrombosis in patients with IBD. Arterial embolism is much less frequent. In patients with IBD, coagulation and fibrinolysis are activated due to acute and chronic inflammation. When patients with IBD are in clinical remission, they still remain at risk for thromboembolic events. Extensive colonic involvement has been associated with these disorders. Genetic factors including hypercoagulability, such as Factor V Leiden, Factor II mutation, or the MTHFR gene mutation, have been studied in patients with IBD. Increased levels of homocysteine have been detected in patients with IBD as compared to controls. In addition, B12 deficiency and folate deficiency may indeed aggravate hyperhomocysteinemia. All hospitalized and immobilized patients with IBD should be treated with low dose heparin for prophylaxis.

**Pulmonary Manifestations**

Pulmonary manifestations in patients with IBD are recognized somewhat less frequently than other manifestations. Several studies have shown empiric pulmonary function with disturbance in diffusing capacity and up to 50 percent of patients with IBD, even those without respiratory symptoms. These pulmonary features may include upper airway disease, large and small airway manifestations, and parenchymal disease, such as that seen with cryptogenic organizing pneumonia. One possible link between pulmonary disease as an extraintestinal manifestation of IBD might be the common embryologic of the GI and pulmonary epithelium from the primitive foregut. In general, patients with UC are at a higher risk of developing these manifestations compared to those with CD.

The most common pulmonary involvement with these conditions is bronchiectasis, followed by chronic bronchitis. Chest radiography is fairly nonspecific, but when high resolution CT is done, a physician commonly finds dilated airways and bronchial wall thickening in these affected patients. Upper airway disease may include subglottic stenosis and a diffuse tracheitis. The bronchiolitis obliterans with organizing pneumonia (BOOP) is the most frequent manifestation of parenchymal pulmonary disease. These patients have fever, cough, and dyspnea. Radiographs reveal patchy opacities, whereas CT will show scattered unilateral or bilateral foci of consolidation and centrilobular nodules. Methotrexate is used to treat inflammatory bowel disease, and a hypersensitivity pneumonitis and occasional pulmonary fibrosis may be seen. In addition, serositis presenting with pleural effusions, pericarditis, pleural pericarditis or myocarditis can develop as a result of drug therapy for IBD. Depending on the type of pulmonary manifestation, any drugs that could be remotely responsible must be withdrawn immediately. Typically pulmonary symptoms either induced by the disease or by its specific treatments, show good response to inhaled corticosteroids. IV steroids may be necessary as well.

Some less common pulmonary features associated with IBD can include a chronic suppurative bronchitis, subglottic stenosis, necrobiotic nodules within the lung parenchyma, chronic bronchiolitis, and pulmonary infiltrates with eosinophilia. In addition, it appears that some patients with concomitant IBD may also have pulmonary sarcoidosis. Both diseases have an association with HLA A3, B8, DR3. Parenchymal lung disease in Crohn’s follows the onset of bowel symptoms with a delay ranging anywhere from 1 to 19 years. However, pulmonary symptoms have been reported to predate the intestinal manifestations of these diseases. With Crohn’s disease, fistulae can develop anywhere throughout the GI tract, and these sinus tracts have been noted to communicate with the airway and parenchyma from the esophagus, ileum, or colon. This rare phenomenon should be considered in any patient with active intestinal disease who has recurrent pneumonia of unclear cause.

Part of the treatment plan for IBD may include mesalamine products or 5-ASA. These compounds are used to treat both ulcerative colitis and Crohn’s. An increase in cough and exacerbation of asthma has been noted with these drugs. Pharyngitis, sinusitis, and chest pain are also more frequently seen in those taking these medications compared to placebo. A very rare lymphocytic alveolitis has been reported with the use of mesalamine. Mesalamine has also been implicated in both acute and chronic eosinophilic pneumonia. Infliximab, a monoclonal antibody directed against anti-tumor necrosis factor alpha, has had a major impact on the treatment of IBD. It is also used to treat rheumatoid arthritis, and sarcoidosis. It has a dramatic effect on granulomatous inflammation. However, it has also been reported to predispose patients to life threatening infection, the most widely publicized being reactivation of tuberculosis. Other opportunistic infections have also been reported.
Renal and Urologic Manifestations

Renal manifestations can occur in anywhere from 4-23 percent of patients with IBD. Several types of glomerulonephritis have been reported including IgA nephropathy, minimal change glomerulopathy, and membranoproliferative glomerulonephritis (MPGN). When the intestinal tract is put into remission, these renal diseases commonly improve. Tubulointerstitial nephritis can be drug induced, such as that with the use of 5-ASA products, but it is also a recognized extraintestinal manifestation of IBD. A rare but serious disorder, more commonly seen with Crohn’s than ulcerative colitis, is amyloidosis. It is characterized by extracellular deposition of proteolytic fragments of serum amyloid A. In the kidney, it presents with proteinuria, which can lead to nephrotic syndrome and renal failure. The main goal to prevent progression of amylosis is to control the underlying inflammatory condition.

The most common renal complication in IBD is nephrolithiasis with a prevalence of 5 to 15 percent. Patients with Crohn’s are more frequently involved. Typically this is in patients that have ileocolonic involvement. Most of these kidney stones are calcium oxalate or uric acid stones. Bile acid malabsorption with fatty acids reaching the colon is the most important cause of calcium oxalate stone formation. As a consequence of free fatty acids binding the calcium within the colon lumen, increased amounts of free oxalate are then reabsorbed, increasing the risk of oxalate stones. Calcium supplementation is recommended. Decreased urine pH as a result of diarrhea and low urine volumes may lead to uric acid stone formation. Therefore, to prevent uric acid stones, fluids are mandatory and a purine reduced diet is encouraged along with alkalinization of the urine. Finally, patients with Crohn’s disease may develop enterovesical fistulae and perivesical abscesses. Obstructive uropathy may occur as a result of retroperitoneal inflammation with fibrosis and scarring in long-term CD. As mentioned, drug-induced renal complications from the 5-ASA products are important. Cyclosporin and tacrolimus can induce acute renal dysfunction as a result of renal vasoconstriction. Glomerulonephritis has been described as a result of anti-TNF therapy.

Anemia

Anemia is a common extraintestinal symptom in patients with IBD, seen in up to a third of patients. One major cause is the chronic disease itself associated with activation of cell mediated immunity. Chronic intestinal blood loss, inadequate dietary intake or malabsorption of iron, B12, folate are reasons for anemia, as well as drug-induced toxicity from medication such as azathioprine or 6-MP or methotrexate.

Iron deficiency anemia can be profound. Iron supplementation can be attempted by mouth, but commonly has to be given intravenously to restore bone marrow function to most of these patients. Occasionally, erythropoietin therapy may be needed. B12 and folate deficiency lead to macrocytic megaloblastic anemia. In Crohn’s disease, this is related to ileal involvement. Deficiencies in B12 can appear up to two years after surgery when extensive storage of B12 in the liver is depleted. Vitamin supplementation, parenterally, is mandatory in these patients.

Metabolic Bone Disease

Osteoporosis and osteopenia are common in patients with IBD (20-50 percent). Hip fractures may be more common in these individuals due to age, steroid treatment, smoking, low physical activity, and inflammatory cytokines. Bone densitometry (DEXA scanning) helps define the presence of osteoporosis. Factors contributing to osteopenia and osteoporosis are the chronic inflammation caused by increased circulating levels of cytokines including IL-1, IL-6, and TNF.
IBD is associated with the malabsorption of calcium and vitamin D, and there may be hypogonadism induced by these conditions. Screening for osteoporosis with a DEXA scan is recommended in patients with chronic corticosteroid use, vertebral fractures, postmenopausal women, or men over the age of 50 with hypogonadism. Preventing bone loss is an important goal in the treatment of these patients. A physician must minimize the use of systemic corticosteroids. Regular supplementation of vitamin D, usually in the range of 1000 international units per day, and calcium 1200 mg per day is suggested. Bisphosphonate therapy, nasal or subcutaneous calcitonin application, and testosterone replacement in hypogonadal men are established approaches to prevent serious bone loss. Weight-bearing, isotonic exercise, the stopping of smoking, the avoidance of alcohol excess, and maintaining adequate dietary calcium are all very beneficial. Raloxifene, a selective estrogen receptor modulator, may reduce or prevent further bone loss.

**Biologic therapies for Extraintestinal Manifestations in IBD—Where do they work?**

The dimeric anti-TNF, IgG monoclonal antibody, infliximab, and the recombinant anti-TNF IgG monoclonal antibody adalimumab, are highly effective agents for the induction and maintenance of remission in moderate-to-severe CD and UC. In addition to clinical response and remission, fistulas commonly will close under these drug influences, along with proven mucosal healing and steroid sparing. The anti-TNF agents have been shown to be effective for a variety of these immune mediated EIMs. Infliximab and adalimumab have been most thoroughly investigated in joint disorders. Physicians see effective treatment for rheumatoid arthritis and psoriatic arthritis with these agents. In addition, there has been proven rapid improvement in peripheral arthritis in IBD patients who had previously been refractory to steroids, 6-MP, Imuran, or methotrexate. The axial arthropathies, especially ankylosing spondylitis and sacroilitis, also may respond. In addition to induction of remission in ankylosing spondylitis, infliximab has been shown to be effective for maintenance of remission. Adalimumab has been shown to be effective for the treatment of ankylosing spondylitis in a recent multicentre randomized double blind placebo controlled trial.

Compared to the numerous anti-TNF treatment trials in joint disease, there have been very few looking at the effective treatment of the muco-cutaneous diseases in IBD. However, there appears to be a very positive experience with pyoderma gangrenosum (PG) and erythema nodosum (EN) with both anti-TNF inhibitors at a variety of dose interval sequences. There have been reports of response in Sweet's syndrome, as well as that seen with the very ominous metastatic cutaneous Crohn's disease. Multiple case reports have highlighted the efficacy of both infliximab and adalimumab for psoriasis. As in IBD, psoriatic patients are prone to developing joint disease, there have been very few looking at the effective treatment of ankylosing spondylitis in a recent multicentre randomized double blind placebo controlled trial. The anti-TNF agents have also been used to treat a variety of ocular conditions associated with IBD. Both agents can suppress uveitis and episcleritis.

**Rare Extraintestinal Manifestations (EIM) of IBD**

**Metastatic Crohn’s disease** is a rare complication of CD with features of cutaneous involvement. Noncaseating granulomas will be seen. There may be a granulomatous perivasculitis. Ulcerating nodules in the skin folds of the anterior abdominal wall and inframammary regions may be seen. Physicians have also seen this in the vulva, penis, ankles, and knees. The bronchial tree and pancreas may be involved. Treatments with steroids are effective and other investigators have used Imuran, cyclosporin, and infliximab.

**Myelodysplastic syndrome (MDS)** may develop in IBD. The pathogenesis here is unclear. Circulating cytokines may be a factor. TNF-alpha may be of great significance with this syndrome. Abnormal neutrophils and/or lymphocytes found in patients with myelodysplastic syndrome may predispose them to chronic infections and bowel inflammation and increase the risk of IBD. MDS should be taken into account in IBD patients who have a normochromic and normocytic anemia that is otherwise unexplained.

**Osteonecrosis,** also termed aseptic necrosis of bone, can involve multiple joints. The femoral heads are most commonly involved, followed by the femoral condyles, proximal humerus, and talus. The prevalence rate in Crohn’s is less than one percent. Although many of these cases are associated with corticosteroid therapy, this is not a prerequisite. Patients with severe GI disease may be more susceptible. The concurrent use of TPN with corticosteroids seems to place the patient at an additional risk for the development of osteonecrosis. The mechanism of steroid-induced osteonecrosis is unclear. It may be a multisystem illness that impairs osteoblast function and increases susceptibility by a second hit from that such as corticosteroids. Bone scans are very helpful here if the disorder is suspected. MRI will complement the detection, and the treatment is usually very unsatisfactory. Additional treatment is protected weight-bearing, although core decompression in combination with bone grafts may be needed. Arthroplasty is the most widely used therapeutic method.
There are no controlled trials evaluating the efficacy of the anti-TNF agents in PSC. Although PSC may represent an immune-mediated disorder, the immunomodulators have not seemed to alter the disease progression. One uncontrolled report suggested that infliximab may improve liver injury in patients with PSC, but there is no data to suggest it changes bile duct anatomy or histologic improvement within the liver. Whether infliximab alters the natural course of PSC remains unstudied at this time.

Summary of the Biologics

There is a significant body of evidence in favor of infliximab and adalimumab in the treatments of IBD and its extraintestinal manifestations. It also implies that the pathogenesis of intestinal and extraintestinal inflammation in IBD share a common TNF- alpha dependent mechanism. TNF- alpha is more likely an essential proinflammatory mediator of a systemic immune response and, thus, its inhibition by these agents could at least partially explain the observed whole body benefits of these drugs in IBD. The introduction of the anti-TNF neutralizing antibodies in clinical practice in the last 18 years has proved to be one of the most significant advances in the care of IBD patients. The successes of these TNF alpha inhibitors have become the inspirational model for numerous other targeted biologic agents (e.g. anti-integrins, JAK inhibitors) that are now available in our armamentarium to treat these aggressive diseases.

Conclusion

With the high prevalence of extraintestinal manifestations and complications in inflammatory bowel disease, which in some cases are more incapacitating than the intestinal disease itself, IBD is truly a systemic disease. As nearly every organ can be affected by extraintestinal manifestations of IBD, early recognition and adequate treatment is necessary to prevent severe morbidity and mortality. In the extraintestinal disorders that follow intestinal activity, such as erythema nodosum or the type 1 arthropathies, treatment of the underlying intestinal disease is often sufficient for rapid relief of symptoms. In the disease independent manifestations, different strategies are clearly needed to optimize the treatment and management. These extraintestinal complications should be assessed in patients with inflammatory bowel disease on a regular basis, as prevention and specific treatments may have a major benefit on quality of life.
References


**Introduction**

Crohn’s disease is a lifelong disease affecting the entire GI tract. The symptoms wax and wane. Medical therapy remains the treatment of choice. Complications, side effects of the disease, and failure of the medical treatment in a symptomatic patient leads to surgical intervention. All the treatment modalities treat the current acute symptoms without curing the disease. Even with ever-evolving, new treatment options, 70 percent of these patients will need some type of surgery over the 10, 20 and 30 year period. Additionally, 30 to 70 percent will require some type of re-operation. Approximately 85 percent of these patients will have disease recurrence within one year. Therefore, at any surgical intervention a physician must conserve intestine as much as possible. Aggressive medical treatment helps in these post-op patients to avoid repeat surgery. One of the main goals of medical treatment is to avoid and prevent surgery. From the patient perspective, it is important to treat urgently an imminent complication, rather than wait for fistula, abscess or perforation to happen. The complication rate from surgery after the disease is allowed to progress escalates to almost 49 percent in these patients, compared to 12 percent in the general population. The serious consideration for surgery in these patients at an appropriate time will reduce the symptoms and complications, while improving the quality of life.

**Distribution of disease:**

1. Ileocolic area ................. 55 percent
2. Colon involvement .............. 19-51 percent
3. Jejunoileal disease ............. 10-20 percent
4. Anal and Perianal involvement .... 4-80 percent
5. Duodenal Crohn’s ............. 1-2 percent

**Indications for surgery:**

- Obstruction is the most common complication. Chronic inflammation of the intestine results in fibrotic changes. These result in strictures, causing obstruction.

- Crohn’s disease can cause abscess formation. This can be intraperitoneal, intramesenteric or retroperitoneal. The abscess can be present in between many loops of bowel. Patients with Crohn’s disease are also prone to get fistula formation. Fistulous communication in Crohn’s disease is known to occur as internal or external. External are enterocutaneous and perianal. Internal are enterovesical, enterovaginal and enteroenteric and rarely impact other organs.

- Diseased segments of intestine can result in adhesions and inflammation leading to perforation. Transmural ulcers and toxic colitis can result in perforation, as well. Less commonly, patients can have hemorrhage. This is a sudden event resulting from erosion into mucosal or submucosal vessels.

- Colon involvement can present in different forms. Carcinoma can start in polyp or from dysplasia of mucosa in the colon. Risk increases after about 10 years of presence of disease. Toxic megacolon occurs secondary to severe inflammation. Carcinoma of the small intestine, however, is much less common.

- Other extra-intestinal manifestations can be seen presenting as peptic ulcers, gallstones, Renal stones, hydronephrosis and dermal manifestations. Growth retardation can also be seen in the pediatric population. After adequate medical therapy and proper nutrition, if there is growth retardation, surgery should be considered and performed prior to closure of epiphyses.

**Treatment of surgical complications:**

**Pre-op Preparation:**

If it is not an emergency and it is an elective or semi elective procedure, the patient should be medically optimized. The following factors tremendously aid in the recovery of a Crohn’s patient from surgery. The patient should be properly hydrated. Electrolytes, hemoglobin and coagulation factors should be corrected as much as possible. Nutritional status should be addressed in patients who are severely malnourished.
by administering TPN for about five days. In a moderately nourished patient, TPN use is controversial. Immunosuppressive agents should be stopped. However, studies suggest that patients treated with biologicals within two months do not have an increased risk of complication. Steroids should be administered if the patient has received steroids in the past six months. Bowel preparation and antibiotics should be given according to the individual institution’s protocol. Institutions have varying protocol for cleaning the colon. Options include giving an enema, Golytely, Miralax and some other available agents.

Operative Procedures and Techniques:

If the abdomen is explored for Crohn’s disease, a physician must examine the entire intestine, as there may be other areas affected by the disease. Sometimes this can be a very challenging task, especially in a patient who has undergone multiple previous surgeries.

Laparoscopic or Open Technique:

The most common laparoscopic procedure performed in Crohn’s disease is surgery of the ileocolic segment. Laparoscopic procedures in general have been shown to have better cosmetic results, less post-operative pain and fewer adhesions leading to less recurrence of obstruction, shorter post-operative ileus, a faster return to work and fewer post-operative pulmonary complications. The duration of the hospital stay depends on the extent and severity of the disease. However, most of the studies prove that duration of the stay is shorter with laparoscopic technique.

Hand assist devices have further facilitated laparoscopic procedures. There are some limiting factors for laparoscopic surgery. These include dense adhesions, complex fistulas and abscesses, and severely ill and unstable patients. Laparoscopic procedures do take longer operative time. Surgeons experienced in laparoscopic surgery have used single incision laparoscopic colectomy, as well. In single incision procedures, ergonomics are more difficult and depend upon the surgeon’s level of training and confidence.

Obstruction:

The most common cause of obstruction is stricture formation. In repeat surgery, adhesions can also be a factor. For long or multiple strictures in close proximity, the choice of procedure is resection and primary anastomosis. However, in patients with short bowel syndrome, even with a long stricture, a strictureplasty should be considered. Strictureplasty should also be considered if the patient has repeat and frequent episodes of bowel obstruction. Short strictures, even if multiple, can also be treated with strictureplasty. The technique requires dividing the stricture area longitudinally for about one to two centimeters proximal and distal to the stricture and closing it transversely. Another technique is to perform Finney type repair, in which a long incision is made at the long segment of the stricture. This is then closed by bringing the open loop in U shape and anastomosing the opening in U shape.

A physician can use the Jaboulay type technique if the stricture area is too long. This is to bring the large loop of stricture area in U shape. Then making an opening just proximal and distal to the stricture area and anastomosing these side by side.

A third technique is a side-to-side isoperistaltic Michelassi strictureplasty. This is performed if there are multiple strictures in a long segment. With this technique the diseased bowel segment is isolated, a proximal loop is placed on top of the distal loop in a side-to-side fashion, and they are anastomosed in two layers. Balloon dilatation with balloon catheter has sometimes been proven to be helpful in patients with short bowel. Balloon dilatation has better outcomes in patients with stricture from previous anastomosis. However, balloon dilatation carries a risk of perforation, bleeding and stricture reoccurrence. Recurrence, even after resection, can be 30 percent at 10 years and can reach up to 50 percent over a 15 year period. Stricture can occur at a different location and not at the site of previous strictureplasty.

Conservative resection is the norm. Even in involvement of the colon, a physician should perform conservative resection so that ideally the patient can be colostomy free for many years. Margins of resection do not have to be microscopically disease free, so long as macroscopically it appears to be disease free. There have been several studies debating the anastomosis technique. The anastomosis can be hand sewn or stapled. It can be side-to-side, end-to-side or end-to-end. There is the same recurrence rate irrespective of anastomosis technique. However, in a severely diseased segment or if there is marked luminal discrepancy, a hand sewn anastomosis ensures a smaller chance of complication. When meticulously performed, a strictureplasty has the same incidence of recurrence as that of resection. One must be aware that an albumin level below 2.0 can result in infectious complications and non-healing. The stricture site should not have active infection at the site of obstruction. In such cases it would be best to divert the flow via a stoma. There have been reports of cancer developing at the site of stricture. Therefore, in suspicious areas, a biopsy should be performed. If there is even dysplasia, a resection must be carried out. Strictureplasty should not be attempted in the presence of infection, perforation, abscess, presence of phlegmon, dysplasia, any internal or external fistula and severe hypoalbuminemia, such as less than 2.0 g/dL.

A short segment of intestine with single or multiple strictures and colonic strictures is best treated with resection. In rare cases a duodenal stricture will present as high grade upper GI
obstruction. These have been treated with gastrojejunostomy and duodenoojejunostomy. However, a bypass procedure carries significant long term complications. Therefore, Heineke-Mikulicz type strictureplasty is preferred if feasible surgically. Colonic strictures can be resected. Benign colonic strictures can also be treated with a self-expanding stent.

Abscess formation:

A patient presenting with sepsis secondary to peritonitis needs to go to the operating room for definitive care. However, most of the time that is not the case and the patient presents with phlegmon or contained perforation. These should be drained either under CT or ultrasound guidance. Many will resolve with additional antibiotics, nutrition supplement and hydration. If these measures fail, these patients will go for surgical resection. Resection of the diseased segment is the treatment of choice. If the severe acute inflammation with phlegmon is close to major vessels, it should be treated by exclusion of the diseased segment. These should be followed by definitive resection, as the rate of malignancy in the bypassed segment is higher. If the bypassed segment is long, one should consider bringing out the proximal end of the bypassed segment as mucous fistula. If the abscess involves multiple loops, it will need to have surgical intervention. The key is to spare and save the length of the bowel. If the abscess is more extensive, it is better to divert and let the infection and sepsis clear and save the length of the bowel. In some patients an abscess eroding to the psoas region can result in compression of the ureter. This will cause hydronephrosis. It will require resection for definitive treatment.

Fistula:

Enteroenteric Fistula:

Even though 30 percent of Crohn’s patients get fistula, this in itself usually does not require surgery. Enteroenteric fistula may remain asymptomatic and can be found on laparotomy. However, a communication between proximal to the distal loop can cause diarrhea, malabsorption. In these cases, a physician encounters fistulous communication between distal ileum to proximal jejunum needing resection. Some patients will develop enterocutaneous fistula at the abdominal scar from previous surgery or a site of previous abscess drainage. Most of the time the drainage is small and patients are reluctant to go for surgery. These will need to be excised on an individual basis.

Genitourinary tract fistula:

Enterovesical and enterovaginal fistulae will need to be addressed surgically by resection of the diseased segment. Enterovesical fistula can lead to pyelonephritis, further affecting the kidneys. Enterovaginal fistula will affect personal hygiene and can cause severe perineal skin excoriation. The low lying rectovaginal fistula or the more-commonly found anointroitus fistula can be approached by creating a transanal flap over the fistula and applying a bioplug, available from different manufacturers, in the fistula tract. The procedure can be repeated if the initial procedure fails. Also, bioplug have been used to close these fistulae. In difficult cases, such as in mid and low rectovaginal fistula, laparoscopically omental flap reconstruction of the rectovaginal space can be a decisive therapy. In treating these, a physician must exclude other common etiologies of diverticular disease, as well as colonic and gynecologic malignancy.

Perianal and Perineal fistula:

Fistulas in the perianal and perineal area are common in Crohn’s disease if the rectum is involved. A combination of rectal disease of the Crohn’s with anal fistula invariably leads to proctocolectomy. Spontaneous healing of fistulae has occurred after resection of the intestine, even when the disease does not involve the colon or rectum. Many of these cases progress from perianal abscesses into fistula. These must be drained. Superficial fistulas may be unroofed to avoid abscess formation.

Deep fistulas cross the sphincter. The fistulotomy may result in incontinence. Therefore, these can be treated with draining setons loosely applied in the tract. These prevent abscess formation, but rarely heal.

Bioabsorbable xenograft anal plugs from Surgisis and Gore have been used to plug the tract and the fibrotic reaction closes the fistula. When all of these fail, a rectal advancement flap may be used to close the internal opening of the fistula. In some cases, one may have to divert the fecal stream either via temporary or permanent colostomy after proctocolectomy.

Perforation:

This is a rare event. Besides the disease itself, a distal obstruction or transmural ulcer in toxic colitis can also result in perforation. Some will heal by adhesions to the adjacent structures. When a free intraperitoneal perforation occurs, the general condition of the patient will change suddenly. Most of these patients with free intraperitoneal perforation will need to go to the operating room. These require resection and peritoneal lavage.
Hemorrhage:

This is a rather uncommon event. Usually there are minimally bloody stools, but hematochezia is not severe enough to require surgical intervention or transfusion. However, some chronic bleeding can cause persistent anemia. Significant hemorrhage may be difficult to diagnose. Physicians need to use bleeding scans, angiography and endoscopic procedures to try to localize the site of bleeding. Unfortunately these techniques are often unable to find the exact locations of bleeding. Sometimes a physician has to resort to intraoperative enteroscopy or colonoscopy to ascertain the site of bleeding, with a surgeon helping to advance the scope.

Carcinoma:

Crohn’s disease is a precancerous disease and the patient will have a 4-20 times higher chance of developing cancer in the affected portion of the intestine. However, the incidence of small bowel cancer, in general, is so low that very few patients will have the disease. The most common site for adenocarcinoma of the small intestine is in the distal ileum. Any stricture must be examined to exclude the possibility of carcinoma or dysplasia. The diagnosis of small bowel carcinoma remains a challenge. Many of these patients will be diagnosed at the time of laparotomy or in the resected specimen. The incidence increases in the bypassed segment from previous surgery. Therefore, even the non-functioning rectal stump should be either excised or the function restored. There is a 70 percent chance of lymph node involvement at the time of initial diagnosis. Therefore, overall prognosis remains poor. Treatment remains resection for adenocarcinoma of the small intestine or colon. If high grade dysplasia is diagnosed in Crohn’s disease, four patients out of 10 (40 percent) had multifocal dysplasia at remote sites. In view of this, in a low risk, healthy patient, total proctocolectomy should be considered.

Pregnancy and surgery in Crohn’s disease:

Usually these patients plan pregnancy when the disease is inactive. If there is flare, medical treatment is carried out aggressively. For surgical complications, MRI, ultrasound, colonoscopy and other imaging techniques are used, depending upon the severity of the condition. Surgical treatment is carried out based on the diagnosis. These patients do carry a higher chance of developing anorectal suppuration and genitourinary fistulas.

Intestinal transplant:

This a rare, difficult and challenging procedure with potential for rejection even after immunosuppressive drugs. It should only be performed in a highly selected patient who has rather terminal bowel disease. Most of the intestine has been resected prior to the transplant. There have been case reports of patients developing Crohn’s disease eight years post-transplant in the transplanted intestine.

Conclusion:

Even with the advent of ever-evolving newer drugs and medical management of Crohn’s disease, surgery remains an integral part of treatment to help patients improve and continue with a better lifestyle. Management should be carried out in close association with a gastroenterologist. As much as possible, surgeons should use bowel sparing procedures via minimally invasive techniques. Aggressive surgical treatment should be carried out in conditions causing septic complications.
**References**


The Role of a Primary Care Physician in the Management of Inflammatory Bowel Disease

Background:
The Duval County Medical Society (DCMS) is proud to provide its members with free continuing medical education (CME) opportunities in subject areas mandated and suggested by the State of Florida Board of Medicine to obtain and retain medical licensure. The DCMS would like to thank the St. Vincent’s Healthcare Committee on CME for reviewing and accrediting this activity in compliance with the Accreditation Council on Continuing Medical Education (ACCME).

This issue of Northeast Florida Medicine includes an article, “The Role of a Primary Care Physician in the Management of Inflammatory Bowel Disease” authored by Bharat K. Misra, MD, which has been approved for 1 AMA PRA Category 1 credits™. For a full description of CME requirements for Florida physicians, please visit www.dcmsonline.org.

Faculty/Credentials:
Bharat K. Misra, MD is a physician with Borland-Groover Clinic in Jacksonville, FL.

Objectives:
1. Screen and treat patients for osteoporosis, depression, anxiety, abnormal body image and nutritional deficiency.
2. Minimize NSAID use in patients with IBD.
3. Minimize antibiotic use in IBD patients and understand the increased risk of clostridium difficile colitis.

Date of release: December 1, 2015  Date Credit Expires: December 1, 2017  Estimated Completion Time: 1 hour

How to Earn this CME Credit:
1. Read the “The Role of a Primary Care Physician in the Management of Inflammatory Bowel Disease” article.
2. Complete the posttest and email your test to Patti Ruscito at patti@dcmsonline.org or mail it to 1301 Riverplace Boulevard, Suite #1638, Jacksonville, FL 32207.
3. You can also go to www.dcmsonline.org to read the article and take the CME test online.
4. All non-members must submit payment for their CME before their test can be graded.

CME Credit Eligibility:
A minimum passing grade of 70% must be achieved. Only one re-take opportunity will be granted. A certificate of credit/completion will be emailed within four to six weeks of submission. If you have any questions, please contact Patti Ruscito at (904) 355-6561 or patti@dcmsonline.org.

Faculty Disclosure:
Bharat K. Misra, MD reports no significant relations to disclose, financial or otherwise with any commercial supporter or product manufacturer associated with this activity.

Disclosure of Conflicts of Interest:
St. Vincent's Healthcare (SVHC) requires speakers, faculty, CME Committee and other individuals who are in a position to control the content of this educations activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly evaluated by SVHC for fair balance, scientific objectivity of studies mentioned in the presentation and educational materials used as basis for content, and appropriateness of patient care recommendations.

Joint Sponsorship Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of St. Vincent’s Healthcare and the Duval County Medical Society. St. Vincent’s Healthcare designates this educational activity for a maximum of 1 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
The Role of a Primary Care Physician in the Management of Inflammatory Bowel Disease

By Bharat K. Misra, MD

Abstract: Primary Care Physicians (PCPs) play an important role in the management of patients with IBD. They should know when to suspect and refer patients with IBD, how to screen and treat for bone loss, update all vaccinations, screen and treat for depression and anxiety, when to consider screening for self-image, and how to monitor and treat nutritional deficiencies. PCPs are critical to optimizing patient care and outcomes.

Introduction

The Primary Care Physician (PCP) plays a very important role in the management of patients with Inflammatory Bowel Disease (IBD), acting much like a copilot to the gastroenterologist, and at times taking over the role of a pilot. Some patients are hesitant to follow up with their PCP, claiming that they have no other medical problems, but most gastroenterologists find that the best outcomes are obtained in patients whose PCP is closely involved with their care. Gastroenterologists sometimes develop a tunnel vision in treating these patients and PCPs can help them in refocusing on the whole patient.

When to suspect IBD and refer patients?

The diagnosis of IBD can be difficult to make. There is no single or specific test that makes a definitive diagnosis of IBD. The diagnosis is based on a combination of clinical findings, laboratory abnormalities, radiological abnormalities, endoscopic findings, pathological features and, more recently, serological markers. The mean delay in diagnosis of IBD was 3.3 years in the past, but has recently decreased to about a year.1 PCPs should be vigilant and refer patients who have symptoms, signs, laboratory or radiological evidence of IBD. The cardinal symptoms are abdominal pain, diarrhea and rectal bleeding. Some patients have tenesmus, anorexia and weight loss. Crohn's disease patients may present with perianal disease or bowel obstruction. These symptoms are usually of gradual onset and may be intermittent. Examination may show mild pallor, non-specific abdominal tenderness, and non-descript perianal disease. Examination however is usually not very impressive. A review of systems may reveal symptoms of extra intestinal involvement. Lab work may be normal or may reveal anemia, hypoalbuminemia, elevated C reactive protein (CRP) or deficiencies of iron, folic acid and vitamin B12. Stool studies may reveal presence of occult blood, leucocytes, lactoferrin and calprotectin. Infectious agents should be ruled out by appropriate stool studies. A family history of IBD may help, but is usually not present. Serological markers of IBD are not very reliable or cost effective in the initial diagnosis.1,2

Osteoporosis screening and treatment

Patients with IBD have a very high prevalence of osteopenia and osteoporosis, which ranges from 18–42 percent.3,4 Osteoporosis is more prevalent in Crohn's disease as compared to ulcerative colitis. Corticosteroid treatment is a major risk factor and the risk of osteoporosis is directly proportional to the lifetime use of corticosteroids. IBD-related chronic inflammation also predisposes to osteoporosis. Hypogonadism, low vitamin D, calcium malabsorption and malnutrition are also contributing factors. Other lifestyle risk factors include smoking, alcoholism, physical inactivity and obesity.5 Postmenopausal women and men over 50 are at increased risk.6 The American Gastroenterological Association (AGA) recommends a Bone Mineral Density (BMD) using a DXA scan of the spine and hip in patients with IBD who are at risk for bone loss and fracture.3 If the BMD is normal, it should be repeated in two to three years. If abnormal, patients should be screened for secondary causes of osteoporosis. Treatment should be initiated
with lifestyle modifications, vitamin D supplementation (800 – 1000 IU daily), calcium citrate (1200mg daily) and pharmacological therapy, such as bisphosphonates. CME

Vaccinations

Because of their disease, chronic inflammation, nutritional deficiencies and use of immunosuppressive medications, patients with IBD are at increased risk for many infectious diseases that can be prevented by proper vaccination. Please refer to the article on vaccinations in this journal.

Treatment of depression, anxiety and screening for abnormal body image

Whether anxiety, depression, stress or certain personality types are predisposing factors for IBD is still unproven and controversial. What is clear is that depression and anxiety are more prevalent in patients with IBD. Symptoms are often worse during disease flares. Health related quality of life outcomes and disease progression is worse in affected patients. Use of corticosteroid medications is a risk factor. Patients with IBD should be screened for anxiety and depression and treated with pharmacological and/or psychotherapeutic measures to obtain the best outcomes.

Body Image is defined as a person’s sense of their physical appearance and bodily function. Recent studies have shown a high prevalence of body image dissatisfaction in patients with IBD, especially in females and those who have had surgery with or without a stoma. Some experts advocate routine screening for abnormal body image.

Monitoring for and treating nutritional deficiencies

Protein calorie malnutrition and macronutrient deficiency is less common in adults with IBD compared to the pediatric population. However, deficiencies of micronutrients are fairly common and the PCP plays an important role in diagnosis and treatment. Deficiencies can occur due to decreased intake, decreased absorption due to disease or surgery, and increased losses from diarrhea or bleeding. Folate deficiency is common, and is seen in 20-60 percent of patients. Decreased dietary intake of folate and the use of sulfasalazine and methotrexate are risk factors. Vitamin B12 deficiency is seen in 25 percent of patients and patients with gastritis, terminal ileal disease and/or resection are at risk. Niacin deficiency is seen in 25 percent of patients, but pellagra is uncommon. Deficiency of fat-soluble vitamins like vitamin A, D, E and K is seen in patients with Crohn’s disease, with fat malabsorption, and with cholestyramine use. Iron deficiency is particularly common, with a prevalence of 35 to 90 percent. In patients with active disease, a ferritin level of below 100 is suggestive of iron deficiency, as ferritin is an acute phase reactant. Many patients are intolerant or unresponsive to oral iron and may require IV iron for adequate replacement. IV iron is preferred in Europe for treating IBD patients. Zinc deficiency is seen in 65 percent of patients, particularly in patients with an ostomy, diarrhea or fistulas. Other mineral deficiencies including selenium, copper and magnesium can be seen.

Patients with IBD should take a multivitamin with minerals daily. Routine lab work can screen for micronutrients and replacement can be initiated when a deficiency is found.

NSAIDS and IBD

While subclinical nonsteroidal anti-inflammatory drug (NSAID) induced injury to the gut is common, symptomatic disease is uncommon. NSAIDs can cause erosions, ulcerations, strictures, diaphragms and colitis, which can sometimes mimic IBD. NSAIDs can also precipitate preexisting IBD. Long term NSAID use appears to be the most risky. These lesions resolve after NSAID use is discontinued and this is one way to distinguish NSAID-induced lesions from lesions due to IBD. COX 2 (Cyclooxygenase 2) inhibitors also carry the same risks, but somewhat less than non-selective NSAIDS. Tylenol, topical NSAIDs and tramadol appear to be safe alternatives for pain control. Narcotics do not exacerbate IBD, but carry the risk of dependence in young patients with chronic symptoms. The main treatment of NSAID-induced gut injury is discontinuance of the offending agent.

Smoking and IBD

Smoking has a deleterious effect on Crohn’s disease, increasing the risk of flares, immunosuppressive drugs and surgery. This risk is higher in females, especially those
with ileal disease.\textsuperscript{19} Hence, patients with Crohn’s disease should be strongly encouraged to stop smoking.\textsuperscript{20,21}

On the other hand, smoking cessation appears to be detrimental in ulcerative colitis. The increased risk of UC can start two years after quitting and last up to 20 years.\textsuperscript{20} Nicotine patches may help symptoms of UC, but a recent study failed to show significant benefit to smoking in UC.\textsuperscript{21} Given the adverse cardio pulmonary effects of smoking, patients with UC should nevertheless be encouraged to quit, and discouraged from starting.

### Clostridium Difficile Infection (CDI) and IBD

Infections with Clostridium difficile (CDI) and other enteric pathogens, account for about 10 percent of IBD flares and relapses.\textsuperscript{22} Concurrent with the nationwide epidemic of CDI, many institutions are reporting an increase in CDI in patients with IBD. These patients are at increased risk for hospitalizations and complications.\textsuperscript{23} One study showed a colectomy rate of about 20 percent.\textsuperscript{23} Risk factors for CDI include antibiotic use and recent hospitalization. CDI cannot be distinguished from IBD endoscopically; diagnosis is based on stool testing. Immunosuppressive drugs should be withheld until stool studies are negative for pathogens. When diagnosed, CDI should be treated with metronidazole or vancomycin, according to current recommendations.\textsuperscript{24} Some patients will develop recurrent CDI, which can be difficult to eradicate. Reports about the safety and efficacy of a novel treatment, Fecal Microbiota Transplantation (FMT) in immunocompromised patients are encouraging.\textsuperscript{25} The study included patients with IBD on immunosuppressive therapy.

### Conclusion

In conclusion, the diagnosis and treatment of IBD remains complex and multifaceted. PCPs play an important role in the management of these patients to enable the best outcomes. Patients with symptoms and signs suggestive of IBD should be referred to a gastroenterologist. Those patients should be screened for bone loss, depression, anxiety, abnormal body image and nutritional deficiencies. Smoking should be discouraged and the use of NSAIDs and antibiotics should be minimized. \textsuperscript{\textcopyright}
References

1. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis/ Crohn's disease in adults [Internet]. Waltham (MA); 2015 Sept. Available from: www.uptodate.com


The Role of a Primary Care Physician in the management of Inflammatory Bowel Disease

CME Questions & Answers (circle one answer)/Free to DCMS Members/$55.00 charge non-members*

(Return by December 1, 2017 BY MAIL: 1301 Riverplace Blvd. Suite 1638, Jacksonville, FL 32207 or ONLINE: www.dcmsonline.org.)

1. A 26-year-old Caucasian female presents to you with symptoms of abdominal pain, diarrhea, rectal bleeding and low back pain for 8-12 months. She has no known medical problems. She denies overseas travel, antibiotic use or NSAID use. Physical examination shows mild tenderness in the right lower quadrant. Lab work shows anemia and elevated CRP. What should be the next step?
   a. Order an IBT panel by Prometheus lab.
   b. Order a CT scan of the abdomen and pelvis with oral and IV contrast.
   c. Refer to a gastroenterologist.
   d. Treat with Levaquin and Flagyl for 10 days and assess response.
   e. Prescribe a fiber supplement, probiotics and hyoscymine for four weeks and then reassess the patient.

2. Which of the following tests is diagnostic of Crohn’s disease?
   a. Very high CRP (C Reactive Protein).
   b. Positive IBT panel for Crohn’s disease.
   c. A small bowel follow-through showing narrowing of the terminal ileum.
   d. Colonoscopy showing multiple ulcers in the cecum and terminal ileum.
   e. None of the above.

3. In patients with IBD, the main risk factor for osteoporosis is:
   a. Physical inactivity.
   b. BMI (Body Mass Index) above 30.
   c. Smoking.
   d. Corticosteroid use.
   e. Alcoholism.

4. A 30-year-old Caucasian male with a 10 year history of ulcerative colitis (UC), presents with “low energy” and intermittent cramping and bloating. He reports interpersonal problems at work. His gastroenterologist has told him that his disease is under control with mesalamine and azathioprine. Examination is unremarkable. Lab work shows mild anemia and normal CRP. You should:
   a. Reassure him that he is doing well.
   b. Refer him back to his gastroenterologist to try infliximab (Remicade).
   c. Refer him to a psychiatrist.
   d. Screen for depression and, if positive, treat with medications.
   e. Refer him to a different gastroenterologist for a second opinion.

5. A 50-year-old African American male with a history of Crohn’s disease presents for the evaluation of malaise and occasional tingling and numbness in both feet. He has a remote history of “bowel resection.” He is on no medications for his Crohn’s disease. Examination is unremarkable. Lab work shows a normal CBC, Chem12 and CRP. Your next step should be:
   a. Reassurance
   b. Referral to a neurologist
   c. Check a serum B12 and folate level
   d. Prescribe a therapeutic multivitamin twice a day for 3 months
   e. Check serum ferritin, iron saturation and TIBC

6. A 45-year-old Caucasian female presents to you for evaluation of intermittent knee and ankle pains, after playing tennis. Symptoms are intermittent and stable over six months. She has a history of severe Crohn’s disease for 10 years; in remission on infliximab (Remicade) for four years. Examination is unremarkable. Her BMI is 32 kg/m2. Lab work shows a normal CBC, Chem12 and CRP. Your recommendations are:
   a. Acetaminophen 500-1000mg four times a day, as needed. Patient continues playing tennis and adds bicycling or swimming.
   b. Ibuprofen 400-800mg four times a day, as needed. Patient stops playing tennis.
   c. Celecoxib (Celebrex) 200mg daily. Patient stops playing tennis and considers bicycling or swimming.
   d. Refer patient back to her gastroenterologist to increase the infliximab (Remicade) dose.
   e. A short course of oral steroids.

7. Regarding smoking and IBD, all of the following statements are true except:
   a. Smoking increases the risk of flares in Crohn’s disease.
   b. Quitting smoking may exacerbate ulcerative colitis.
   c. Smoking increases the risk of surgery in Crohn’s disease.
   d. The risks of smoking are highest in women with ileal disease.
   e. Patient with ulcerative colitis should be encouraged to continue smoking, but in moderation.

8. A 25-year-old Caucasian female with ulcerative colitis presents with abdominal pain, diarrhea and rectal bleeding for two weeks. Her colitis has been in remission on adalimumab (Humira) 40mg SQ every two weeks. She denies overseas travel. She was given oral amoxicillin for a dental procedure six weeks ago. Examination reveals evidence of mild dehydration and mild abdominal tenderness. Your next step is:
   a. Start Prednisone 40mg daily and refer her to her gastroenterologist.
   b. Start Ciprofloxacin and Metronidazole for 10 days.
   c. Check stools for bacterial culture and Clostridium difficile and hold adalimumab (Humira) until the results come back.
   d. Consider a flexible sigmoidoscopy in the office.
   e. Start mesalamine 250mg four times a day for 10 days. Continue adalimumab (Humira).
REACHING 2,500+

including hospitals, physicians, residents, dermatologists, ophthalmologists, urologists, rheumatologists, surgeons, local, state, and national elected officials, government agencies, and other affiliated healthcare professionals! Companies providing services such as home health care, hospice care, insurance, marketing, medical equipment & supplies, outpatient surgery, pharmacies, physical therapy, and more!

Tablet/Mobile access delivers a +41% lift in ad awareness and a +10% lift in brand favorability

Digital versions of Northeast Florida Medicine Journal deliver traditional media to an audience with an increasing appetite for new digital content. Online readership moves content to new levels with instantaneous, 24/7 accessibility and unmatched sharing capability. One interested reader can deliver articles and advertisements to colleagues and friends, bringing multitudes of new views and subscribers. And research shows that an increased online readership increases print only readership expanding the benefit even further.

ADVERTISING RATES

<table>
<thead>
<tr>
<th>SIZE</th>
<th>B &amp; W</th>
<th>COLOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back Cover</td>
<td>$1,299</td>
<td></td>
</tr>
<tr>
<td>Inside Covers</td>
<td>$999</td>
<td></td>
</tr>
<tr>
<td>Page 1</td>
<td>$899</td>
<td></td>
</tr>
<tr>
<td>Page Facing IBC</td>
<td>$799</td>
<td></td>
</tr>
<tr>
<td>Page 2-5</td>
<td>$799</td>
<td></td>
</tr>
<tr>
<td>Facing CME Test</td>
<td>$799</td>
<td></td>
</tr>
<tr>
<td>Full Page</td>
<td>$799</td>
<td></td>
</tr>
<tr>
<td>1/2 Page</td>
<td>$699</td>
<td>$599</td>
</tr>
<tr>
<td>1/4 Page</td>
<td>$399</td>
<td>$499</td>
</tr>
<tr>
<td>Insert (preprinted)</td>
<td>$699</td>
<td>$699</td>
</tr>
</tbody>
</table>

Contact E&M Consulting, Inc. regarding Advertising Sales
800.572.0011 / 904.371.2916 / rob@emconsultinginc.com
IMPORTANT SAFETY INFORMATION FOR REMICADE® (infliximab)

SERIOUS INFECTIONS

Patients treated with REMICADE® (infliximab) are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue REMICADE® if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before and during treatment with REMICADE®. Treatment for latent infection should be initiated prior to treatment with REMICADE®.

- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients may present with disseminated, rather than localized, disease. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with REMICADE® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with REMICADE®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy, who are on treatment for latent TB, or who were previously treated for TB infection.

Risk of infection may be higher in patients greater than 65 years of age, pediatric patients, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant therapy. In clinical trials, other serious infections observed in patients treated with REMICADE® included pneumonia, cellulitis, abscess, and skin ulceration.
BEYOND MILD?
GET SERIOUS
WITH REMICADE® (infliximab)

She may be moderate, but she wants her uncontrolled symptoms taken seriously.

REMICADE® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease (CD) who have had an inadequate response to conventional therapy.

REMICADE® is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

MALIGNANCIES
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE®. Approximately half of these cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including REMICADE®. These cases have had a very aggressive disease course and have been fatal. The majority of reported REMICADE® cases have occurred in patients with Crohn’s disease or ulcerative colitis and most were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE® at or prior to diagnosis. Carefully assess the risks and benefits of treatment with REMICADE®, especially in these patient types.

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with Crohn’s disease, rheumatoid arthritis, or plaque psoriasis may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including REMICADE®, more cases of other malignancies were observed compared with controls.

(CONTINUED ON THE NEXT PAGE)
IMPORTANT SAFETY INFORMATION (CONTINUED)

MALIGNANCIES (CONTINUED)
The rate of these malignancies among patients treated with REMICADE® was similar to that expected in the general population whereas the rate in control patients was lower than expected. Cases of acute and chronic leukemia have been reported with the use of TNF blockers. The potential role of TNF inhibitors in the development of malignancies is not known. Caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD). Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including REMICADE®. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

CONTRAINDICATIONS
REMICADE® is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. REMICADE® should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue REMICADE® if new or worsening CHF symptoms appear. REMICADE® should not be re-administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

HEPATITIS B REACTIONS
TNF inhibitors, including REMICADE®, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients should be tested for HBV infection before initiating REMICADE®. For patients who test positive, consult a physician with expertise in the treatment of hepatitis B. Exercise caution when prescribing REMICADE® for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with REMICADE®. Discontinue REMICADE® in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of REMICADE® and monitor patients closely.

HEPATOTOXICITY
Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in patients receiving REMICADE® postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, REMICADE® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

HEMATOLOGIC EVENTS
Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia (some fatal) have been reported. The causal relationship to REMICADE® therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of REMICADE® in patients who develop significant hematologic abnormalities.

HYPERSENSITIVITY
REMICADE® has been associated with hypersensitivity reactions that occur in a time of onset. Acute urticaria, dyspnea, and hypotension have occurred in association with infusions of REMICADE®. Serious infusion reactions including anaphylaxis were infrequent. Medications for the treatment of hypersensitivity reactions should not be available.

NEUROLOGIC EVENTS
TNF inhibitors, including REMICADE®, have been associated in rare cases with CNS manifestations of systemic vasculitis, seizure, and new onset or exacerbation of CNS demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Exercise caution when considering REMICADE® in patients with these disorders and consider discontinuation if these disorders develop.

AUTOIMMUNITY
Treatment with REMICADE® may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

ADVERSE REACTIONS
In clinical trials, the most common REMICADE® adverse reactions occurring in >10% of patients included infections (e.g., upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

USE WITH OTHER DRUGS
Concomitant use of REMICADE® with anakinra, abatacept, tocilizumab, or other biologics used to treat the same conditions as REMICADE® is not recommended because of the possibility of an increased risk of infection. Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

LIVE VACCINES/ THERAPEUTIC INFECTIOUS AGENTS
Live vaccines or therapeutic infectious agents should not be given with REMICADE® due to the possibility of clinical infections, including disseminated infections.

Bring pediatric patients up to date with all vaccinations prior to initiating REMICADE®. At least a 6-month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to REMICADE®.

For more information, please see full Prescribing Information and Medication Guide for REMICADE®. Provide the Medication Guide to your patients and encourage discussion.

**REMICADE** (infliximab)

**Lyophilized Concentrate for Injection, for Intravenous Use**

**Brief Summary of Full Prescribing Information**

**WARNING: SERIOUS INFECTIONS and MALIGNANCY**

**SERIOUS INFECTIONS**

Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death [see Warnings and Precautions and Adverse Reactions]. Patients who develop these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMICADE should be discontinued if a patient develops a serious infection or sepsis. Reported infections include:

- **Active tuberculosis**, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or progressive disease with a history of positive tuberculin test or history of tuberculosis before REMICADE use and during therapy. Treatment for latent infection should be initiated prior to REMICADE use. 
- **Invasive fungal infections**, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

**MALIGNANCY**

Lymphomas and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE [see Warnings and Precautions].

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTLC), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

**CONTRAINDICATIONS:** REMICADE at doses ≥5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (Heart Failure and Remicade [HFaRe] study), patients treated with REMICADE at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure [see Warnings and Precautions and Adverse Reactions]. REMICADE should not be re-administered to patients who have experienced a severe hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

**WARNINGS AND PRECAUTIONS:**

**Serious Infections:** Patients treated with REMICADE are at increased risk for developing infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacteria, mycobacteria, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystis and tuberculosis have been reported with REMICADE. Patients have frequently presented with disseminated rather than localized disease. Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbidities, and patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection.

The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have received prior therapy in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

**Tuberculosis:** Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients with co-morbidities and those with previous exposure. Treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with REMICADE during treatment for latent tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating REMICADE and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even for patients concurrently receiving anti-TNF therapy. Postexposure prophylaxis therapy should also be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during REMICADE treatment, especially in patients who have previously or recently travelled to an area of the world with high prevalence of tuberculosis. Patients who had close contact with a person with active tuberculosis. Monitoring: Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with REMICADE. REMICADE should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with REMICADE should be closely monitored, under complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

**Invasive Fungal Infections:** For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious septicemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Malignancies: Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with a TNF-blocking agent which initiated therapy. Patients treated with REMICADE, including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The median duration of follow-up was 6 to 8 years. In rheumatoid arthritis patients, 1 lymphomas were observed for a rate of 9.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. In the combination therapy population for ulcerative colitis and Crohn's disease, 2 lymphomas were observed for a rate of 0.05 cases per 100 patient-years of follow-up, which is approximately two-fold higher than expected in the general population.
REMICADE® (infliximab) and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data [see Warnings and Precautions and Adverse Reactions]. Skin cancer: Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including REMICADE [see Adverse Reactions]. Periodic skin examination is recommended for all patients, particularly those with a history of skin cancer. TNF blockers may increase the risk of developing new skin cancers in the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blocking agents compared with control patients. During the controlled portions of REMICADE trials, the malignancy rates were similar for patients with malignancies at some time during their treatment compared with patients with no malignancies at any time during their treatment. In patients receiving REMICADE-treated patients vs. a rate of 0.1/100 patient-years among control patients, with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the majority of malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in the TNF blocker-treated patients compared with control patients. All patients had a history of heavy smoking [see Adverse Reactions]. Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD. Psoriasis patients should be monitored for new-onset malignancy skin cancer, and/or epidermoid in the patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy [see Adverse Reactions]. The potential role of TNF-blocking therapy in the development of malignancies is not known [see Warnings and Precautions and Adverse Reactions]. The risk of malignancy in patients treated with TNF blockers cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy. The safety and efficacy of treatment with REMICADE and other agents that inhibit TNF have been assessed in a small number of patients with a history of malignancy. Treatment with REMICADE and other agents that inhibit TNF have been assessed in a small number of patients with a history of malignancy. Treatment with REMICADE for the treatment of malignancy is not recommended. Use with Anakinra: Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and TNF-blocking agents, and anakinra therapy, similar toxicities may also result from the combination of antithrombin and anakinra. Therefore, the combination of antithrombin and anakinra is not recommended. Use with Abatacept: In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased risk of reactivation of mycobacterial disease. Therefore, the combination of abatacept and TNF-blocking agents is not recommended [see Drug Interactions]. Concurrent Administration with other Biological Therapies: There is insufficient information regarding the concomitant use of REMICADE with other biological therapies used to treat the same conditions as REMICADE. The concomitant use of REMICADE with these biological therapies is not recommended because of the possibility of an increased risk of infection [see Drug Interactions]. Switching Between Biological Disease-Modifying Antirheumatic Drugs (DMARDs): Care should be taken when switching from one biologic to another, since overlapping biological activity is not seen in all cases. Some of these patients have not yet achieved a state of remission. The biological agents are not interchangeable. There is no data specifically to direct therapy. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at 50 mg/kg REMICADE. There have been reports of postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear [see Contraindications and Adverse Reactions]. Hematologic Reactions: Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if signs or symptoms suggestive of infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. Hypersensitivity: REMICADE has been associated with cases of anaphylaxis. Anaphylaxis, including anaphylactic shock, respiratory distress, urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy [i.e., as early as after the second dose], and REMICADE therapy was reinitiated following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, and facial edema and/or dysphagia. These reactions were associated with a marked increase in serum levels of IgG and, in some patients, with detectable anti-Drug antibodies. Infliximab, and possibly loss of drug efficacy. REMICADE should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, and corticosteroids) should be available in the event of a reaction [see Adverse Reactions]. In rheumatoid arthritis, Crohn’s disease and psoriasis clinical trials, re-administration of REMICADE after a period of non-treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment [see Adverse Reactions]. Readministration of REMICADE at the time of disease flare while receiving REMICADE. Hepatitis B Virus Reactivation: Use of TNF blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurred in conjunction with TNF blocker therapy and with hepatitis B virus reactivation, the majority of patients who were considered HBV carriers received other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy, including REMICADE. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV should receive other TNF blocker therapies if hepatitis B reactivation is anticipated. Patients who are carriers of HBV should be monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and anti-viral therapy with appropriate supportive treatment should be initiated. The safety of reactivation of hepatitis C virus in patients treated with TNF blockers is not well known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely. Hepatotoxicity: Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred within 2 weeks to more than 1 year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discontinuation of therapy in many of these patients. Severe or fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, REMICADE should be discontinued, and a thorough investigation of the abnormalities should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury [see Adverse Reactions]. Patients with Heart Failure: REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after careful consideration of the benefit and risk. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at 50 mg/kg REMICADE. There have been reports of postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear [see Contraindications and Adverse Reactions].
brought up to date with all vaccinations prior to initiating REMICADE therapy. The interval between vaccination and initiation of REMICADE therapy should be in accordance with current vaccination guidelines. **ADVERSE REACTIONS: Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in routine clinical practice and may not predict the rates observed in broader patient populations in clinical practice. **Adverse Reactions in Adults:** The data described herein reflect exposure to REMICADE in 4779 adult patients (1804 patients with rheumatoid arthritis, 1180 patients with Crohn's disease, 262 with ankylosing spondylitis, 410 with psoriatic arthritis), and also be present in other forms of RA (including plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. [For information on adverse reactions in pediatric patients see Adverse Reactions.] One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash). **Infusion-related Reactions:** An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of REMICADE-treated patients experienced an infusion reaction compared to 5% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period. Of the REMICADE-treated patients, 3% experienced infusion-related reactions by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiovascular reactions (primarily chest pain, hypotension, hypertension or dyspnea), and 1% were accompanied by pruritis, urticaria, or the combination of pruritis and urticaria. Infusion reactions were also accompanied by nausea, vomiting, chest pain, rash, or diarrhea in 9%. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE, and the initial infusion of REMICADE, or placebo. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo group. There were 4 serious infections in the 10 mg/kg REMICADE treatment groups versus 5 in the placebo group. **Malignancies:** In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients [see Warnings and Precautions]. **Immunogenicity:** Treatment with REMICADE can be associated with the development of antibodies to infliximab. An enzyme immunoassay (EIA) method was originally used to measure anti-infliximab antibodies in clinical studies of REMICADE. The EIA method is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for follow-up test results. The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of REMICADE except for the Phase 3 study in pediatric patients with ulcerative colitis where the incidence of antibodies to infliximab was detected using both the EIA and the ECLIA methods. [see Contraindications and Warnings and Precautions].
are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibody to other products may be misleading.

Hepatotoxicity: Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see Warnings and Precautions). Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE, who are chronic carriers of the virus (see Warnings and Precautions). In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in control groups. Infection was not a common indication in any of these agents. In patients receiving REMICADE as monotherapy or in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

Table 1. Proportion of patients with elevated ALT in clinical trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo %</th>
<th>REMICADE %</th>
<th>Placebo %</th>
<th>REMICADE %</th>
<th>Placebo %</th>
<th>REMICADE %</th>
<th>Placebo %</th>
<th>REMICADE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>24%</td>
<td>34%</td>
<td>5%</td>
<td>9%</td>
<td>4%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>34%</td>
<td>39%</td>
<td>5%</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>17%</td>
<td>16%</td>
<td>5%</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>15%</td>
<td>51%</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>16%</td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Placenta ischemia</td>
<td>24%</td>
<td>49%</td>
<td>9%</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate. Median follow-up was 59 weeks. Placebo patients received methotrexate in Crohn's disease. Placebo patients received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in the table. Median follow-up was 30 weeks. Placebo patients received methotrexate in 39 weeks for placebo and 31 weeks for REMICADE. Median follow-up was 24 weeks for the placebo group and 102 weeks for the REMICADE group. Median follow-up was 39 weeks for the REMICADE group and 16 weeks for the placebo group. ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo.

Adverse Reactions in Psoriasis Studies: During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in death, life threatening, requiring hospitalization, or persistent or significant disability/incapacity) was 0.05% in the 3 mg/kg REMICADE group, 1.5% in the placebo group, and 1.6% in the 5 mg/kg REMICADE group. Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks experienced a 1.5% SAE; 1% in Study II, 4.1% in Study III, and 4.7% in all patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE. One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious adverse reactions and nonserious adverse reactions are reported at least 1 NMSC compared to 0 of 334 patients who received placebo. In the psoriasis studies, 1% (15/1537) of patients experienced serious skin infections or a combination of articular and/or myalgia with fever, and/or rash, usually in the early treatment course. Of these patients, 1 required hospitalization due to fever, severe myalgia, arthritis, and swollen joints, and hospitalization. Other Adverse Reactions: Safety data are available from 4779 REMICADE-treated adult patients, including 1204 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 253 with psoriatic arthritis, 1373 with plaque psoriasis, and 171 with Crohn's disease patients. For information on other adverse reactions in pediatric patients, see Adverse Reactions. Adverse reactions reported in >5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The frequencies and types of adverse reactions observed were similar in REMICADE treatment, ankylosing spondylitis, plaque psoriasis, and Crohn's disease patients except for abdominal pain, which occurred in 29% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.
infection, pharyngitis, abdominal pain, fever, and headache. Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric Crohn's disease study (Study Peds Crohn's) but higher than the proportion in the adult Crohn's disease trials. In adults, infections and abscesses were the second most common adverse event in the PediAPC trial. The incidence of infections in the pediatric UC trial was 13.2% (59/450) in the every 8 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12/760 (1.6%) of all treated patients. In the pediatric UC trial, 83 were evaluable for antibodies to infliximab using the EIA as well as the drug-tolerant ECLIA. With the EIA, 4 of 58 (7%) patients had antibodies to infliximab. With the ECLIA, 30 of 98 (31%) patients had antibodies to infliximab. [See Adverse Reactions, Immune-mediated]. The higher incidence of antibodies to infliximab by the ECLIA compared to the 60-fold dilution ELISA may be related to the different analytical method. While EIA-positive patients generally had undetectable trough concentrations, ECLIA-positive patients could have detectable trough concentrations of infliximab because the ECLIA assay is more sensitive and drug-tolerant. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the remission maintenance trial. ULN elevations >3 ULN, and 2% (1/60) had elevations >5 ULN (median follow-up was 49 weeks). Overall, 8 of 60 (13%) treated patients experienced one or more infusion reactions, including 2 (2%) patients in the every 8-week treatment maintenance group. No serious infusion-related reactions were reported in the pediatric UC trial. In the remission maintenance trial, 7/60 (12 to 17 year age group) and 15 in the 6 to 11 year age group. The numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events. There were higher proportions of patients with infusion reactions in children compared to adults. Children did not appear to have more infusion reactions (40% vs. 16%) in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group (40% vs. 49%), for serious infections, the proportions were similar in the two age groups (15% in the 6 to 11 year age group vs. 11% in the 12 to 17 year age group). Overall proportions of adverse reactions, including infusion reactions, were similar between the 6 to 11 and 12 to 17 year age groups (13%). Post-marketing Experience: Adverse reactions have been reported during post-approval use of REMICADE in adult and pediatric patients. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate the frequency of occurrence or establish a causal relationship to REMICADE exposure. The following adverse reactions, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia [see Warnings and Precautions], interstitial lung disease (including pulmonary fibrosis/intertstitial pneumonia and very rare cases of pneumonitis and pulmonary edema), new or worsening thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), nephrotic syndrome (including its subtypes including pustular, primarily palmpalmar), transverse myelitis, and neuropathies (additional neurologic reactions have also been observed) [see Warnings and Precautions], acute liver failure, jaundice, hepatitis, and cholestasis [see Warnings and Precautions], serious infections [see Warnings and Precautions], bronchiolitis obliterans organizing pneumonia, and adenocarcinoma [see Warnings and Precautions] and vaccine breakthrough infection including bovine tuberculosis (disseminated BCG infection) following vaccination in an infant exposed to urea in infliximab [see Warnings and Precautions]. Infusion-related Reactions: In post-marketing experience, cases of severe bronchospasm, and seizure have been associated with REMICADE administration. Cases of myocardial ischemia/infarction and transient visual loss have also been rarely reported in association with REMICADE during or within 2 hours of infusion. Adverse Reactions in Pediatric Patients: The following adverse reactions and symptomatic increases in the blood count have been observed in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions. Serious adverse reactions in the post-marketing experience with REMICADE in children and adolescents have also included hepatosplenic T-cell lymphomas [see Boxed WARNINGS and Warnings and Precautions], transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies. Drug Interactions: Use with Anakinra or Abatacept: An increased risk of serious infections was seen in clinical trials of patients with rheumatoid arthritis treated with TNF-α-blockers and anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF-α-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNF-α-blockers. Therefore, the combination of REMICADE and anakinra or abatacept is not recommended. [See Warnings and Precautions]. Use with Tocilizumab: The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including REMICADE, should be avoided because of the possibility of increased immunosuppression and increased risk of infection. Use with Other Biological Therapies: The combination of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE is not recommended [see Warnings and Precautions]. Methotrexate (MTX) and Other Concomitant Medications: Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In concomitant medication studies, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In rheumatoid arthritis clinical trials, concomitant medications included MTX in over half of the patients as well as NSAIDs, folic acid, and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations. Immunosuppressants: Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients who did not receive immunosuppressants. However, anti-infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates. Cytochrome P450 Substrates: The formation of CYP450 enzymes may be suppressed by the co-administration of CYP450 substrates and inhibitors. Uridine 5'-diphosphate glucuronosyltransferase (UDPGT) and cytochrome P450 1A2 (CYP1A2, e.g., caffeine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. Live Vaccines/Therapeutic Infectious Agents: It is recommended that live vaccines not be given concurrently with REMICADE because REMICADE therapy can impair the effectiveness of vaccines. Influenza vaccine can be given to infants after in utero exposure to infliximab for at least 6 months following birth [see Warnings and Precautions]. It is recommended that therapeutic infectious agents not be given concurrently with REMICADE [see Warnings and Precautions]. USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category B: It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNF in species other than humans and chimpanzees, animal reproduction studies have not been conducted. Because animal reproduction studies are not always predictive of human response, REMICADE should not be used during pregnancy unless the potential benefit to the mother clearly outweighs any potential risk to the fetus. Infertility: There were no adverse effects in animal reproduction studies. As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the sera of infants up to 5 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection. Infliximab has not been shown to cause harm to maternal or fetal tissues and organs. Infliximab is contraindicated in women who are pregnant or who may become pregnant before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see Warnings and Precautions]. Nursing Mothers: It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. However, because immunoglobulins and other drugs and immunogenic substances are excreted in human milk, REMICADE is not recommended in nursing mothers and because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed their infants while taking REMICADE. 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. Data on the use of REMICADE have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative colitis. However, REMICADE has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. Pediatric Crohn's Disease: REMICADE is indicated for the maintenance of response in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy [see Boxed WARNINGS, Warnings and Precautions, Indications and Usage (1.2) in Full Prescribing Information, Clinical Information, Clinical Studies (14.2) in Full Prescribing Information and Adverse Reactions]. REMICADE has been studied only in combination with conventional immunosuppressive therapy in pediatric Crohn's disease. The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric Crohn's disease has not been established. Pediatric Ulcerative Colitis: The safety and effectiveness of REMICADE for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by data from adequately well-controlled studies of REMICADE in adults. Additional safety and pharmacokinetic data were collected in 60 pediatric patients aged 6 years and older [see Clinical Pharmacology (12.3) in Full Prescribing Information, Dosage and Administration (24) in Full Prescribing Information, Adverse Reactions, and Clinical Studies (14.4) in Full Prescribing Information]. The effectiveness of
REMICADE in inducing and maintaining mucosal healing could not be established. Although 41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the induction phase was open-label and lacked a control group. Only 9 patients had an optional endoscopy at Week 54. In the pediatric UC trial, approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTLC, a careful risk-benefit assessment should be made when REMICADE is used in combination with other immunosuppressants.

The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric ulcerative colitis patients have not been established in clinical trials. Juvenile Rheumatoid Arthritis (JRA): The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease-modifying antirheumatic drugs (DMARDs) was permitted. Doses of 3 mg/kg REMICADE or placebo were administered intravenously at Weeks 0, 2, and 6. Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at Weeks 14, 16, and 26, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with REMICADE for up to 2 years in a comparable extension study. The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults [see Clinical Pharmacology (12.3) in Full Prescribing Information]. A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks compared with 18% (11/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 6 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 8 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg. A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient. Geriatric Use: In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received REMICADE, compared to younger patients—although the incidence of serious adverse reactions in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in REMICADE-treated patients 65 years and older was greater than in those under 65 years of age; therefore caution should be used in treating the elderly [see Adverse Reactions].

OVERDOSAGE: Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. REFERENCES: 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161: S221-S247. 2. See latest Centers for Disease Control guidelines and recommendations for tuberculin testing in immunocompromised patients.

Inflammatory Bowel Disease

Abstract: Patients with inflammatory bowel disease (IBD) show an increased risk of pancreatic diseases compared to the general population, usually taking place in the course of the malady or sometimes even preceding the diagnosis. This particular kind of complication is mainly due to therapeutic agents used in the management of Crohn’s disease (CD), ulcerative colitis (UC), and microscopic colitis (MC). IBD also displays other extraintestinal manifestations involving joints, skin, eyes, kidneys, liver, gallbladder, and lungs. Despite IBD’s unknown etiology, it is believed to be the result of the interaction of genetics, the immune system, and environmental factors. Health care providers and the general population need to identify premature clinical manifestations of pancreatic affliction to delay progression and/or sustain a better management of patients with IBD.

Introduction

Inflammatory Bowel Disease (IBD) includes major entities such as Crohn’s disease, and ulcerative colitis, but microscopic colitis (MC), a minor member, is a surging form of this disease group. Although their etiology is unknown, and they all have distinct clinic and pathological characteristics, the relationship between IBD and pancreatic idiosyncrasies has definitely been established throughout the years.

IBD Classification

Crohn’s Disease

Crohn’s disease is a chronic disorder characterized by transmural inflammatory skip lesions that involve the entire gastrointestinal tract. Its symptoms are unpredictable and may include abdominal pain, cramping, diarrhea, fever, fatigue, anemia, reduced appetite, and weight loss.1

Ulcerative Colitis

Ulcerative colitis is the chronic inflammation of the mucosal layer of the colon. Its most common symptoms include diarrhea, abdominal pain, hematochezia, fatigue, weight loss, reduced appetite, tenesmus, and fever.1,2

Microscopic Colitis

Microscopic colitis is an inflammatory condition of the colon, usually of insidious onset, characterized by non-bloody, watery, chronic diarrhea.3,6 Based on the exhibited histological features, MC is subclassified in lymphocytic and collagenous colitis. Lymphocytic colitis is branded as an intraepithelial lymphocytic infiltrate of >20 cells per high power field, while collagenous colitis shows a subepithelial collagen band >10 micrometers in thickness.3,7-10

Most commonly associated symptoms include fecal urgency/incontinence, abdominal pain, and nocturnal episodes.11,12 Weight loss can be perceived due to fluid loss, mostly in patients with active disease (≥3 stools or ≥1 watery stool daily); some extreme cases may lose up to two liters per day.4,13

Pancreatic Involvement in IBD

The etiology of pancreatic anomalies in IBD appears to be multifactorial. Contributing factors include medication used to treat IBD (6-mercaptopurine, azathioprine, corticosteroids or 5-ASA agents), duodenal fistulas, anatomic abnormalities, such as ampullary and duodenal Crohn’s disease, gallstones, primary sclerosing cholangitis, pancre-
Inflammatory Bowel Disease

atic autoantibodies, and pancreatic cancer."14 Due to the
ominous IBD-pancreas association, periodic assessment
of the pancreatic function in suspected IBD patients is
prudent, as pancreatic involvement may also precede the
onset of IBD.

Pancreatitis

Pancreatitis is a rare extraintestinal manifestation of
IBD. The risk of developing acute15 or chronic pancre-
atitis16 in adults and children with IBD has proven to
be augmented. New data also suggests that autoimmune
pancreatitis, which is less common, arises more often
among this subgroup.17

In IBD patients, pancreatitis is usually clinically silent18
and holds an incidence rate that ranges from 4.8 to 38
in 100,000 inside the U.S.19 Recently, the incidence of
acute pancreatitis (AP) in CD has been reported to vary
from 1 to 1.4 percent during a period of 10 years.19 Con-
currently, Bermejo et al described a 1.6 percent incidence
of AP in IBD patients, with 63.4 percent of the etiology
attributable to medical treatment.20

Furthermore, evidence reveals that AP may denote the
onset of IBD in children and in adults. The prevalence
of AP as a debuting symptom of IBD is 0.06 percent
in adults and 3.6 percent in children.21 Other previous
studies have shown a maximum prevalence of 27 percent
of AP preceding IBD.22,23 Additionally, AP in adults has
been commonly described in CD rather than in UC, but
its severity is similar to that in the general population.15

Idiopathic Chronic Pancreatitis (ICP)

The association of IBD with idiopathic chronic pan-
creatitis has been sporadically reported predominantly in
pediatrics.24-26 Although some patients present with irregu-
lar pancreatograms indicative of chronic pancreatitis, they
are usually asymptomatic even when significant exocrine
insufficiency coexists.27 Therefore, it is not surprising to
find pancreatic fibrosis, acinar regression, and granulomas
in patients with IBD, especially in CD.28,29 On the other
hand, pancreatic duct changes (stenosis) and weight loss
are more likely to happen in UC.29

Exocrine Pancreatic Insufficiency (EPI)

EPI is an extraintestinal manifestation of IBD charac-
terized by deficiency of the exocrine pancreatic enzymes
(amylose, protease, and lipase), resulting in malnutrition.30
Normally, lipase breaks triglycerides into fatty acids and
monoglycerides. Those are solubilized by bile salts, and
ultimately turned into micelles for lipid absorption.31

Detection of EPI is often delayed since fat digestion is
not markedly impaired until lipase output falls below 10
percent and/or malnutrition of fat is clinically perceived as
steatorrhea.32 This is why fat malabsorption precedes that
of proteins and carbohydrates.33 Steatorrhea is also caused
due to bile salt pool reduction (owed to precipitation and
subsequent adsorption to undigested food)34 and due to
neurohormonal disturbances (that result in gall bladder
hypomotility and accelerated gastrointestinal transit).35

The etiology of exocrinopathy in IBD includes pan-
creatic and nonpancreatic causes.36 Pancreatic causes of
EPI include ICP (primary cause) and pancreatic duct
obstructions (like gallstones, pancreatic cancer, or ana-
tomic abnormalities) that thwart pancreatic excretions
from reaching the duodenum. Nonpancreatic causes of
EPI comprise autoimmune pancreatitis37, and surgical
procedures in the gastrointestinal and pancreatic terri-
itories, leading to loss of pancreatic parenchyma and/or
postprandial asynchrony.38

Pancreatic insufficiency is associated to IBD’s activity
and extent, and can be observed in patients with or with-
out a history of pancreatitis.27,39,40 It has been reported in
approximately 18 percent of IBD patients; some studies
even show a 21-80 percent rate of inadequate levels of
pancreatic exocrine secretions in IBD patients.41,42 Hence,
due to its silent insidious nature, fecal elastase-1 levels
should be assessed to determine presence and severity of
exocrinopathy.43

EPI’s management primarily consists of pancreatic
enzyme replacement therapy (PERT), however it also
includes fat-soluble vitamin supplementation, and life-
style adjustments.

Autoimmune Pancreatitis (AIP)

Patients with IBD present up to a 15X increased risk
of AIP compared to the general population. The presence
of IgG4-positive cells on the colon’s mucosa of afflicted
patients may imply that IBD embodies an extrapancre-
atic manifestation of autoimmune pancreatitis; for that
reason almost 6 percent of patients diagnosed with AIP,
also hold a diagnosis of IBD.44
Gallstones

Prevalence of gallstones in UC is approximately 10 percent, which is the same as the general population; nevertheless, in CD, it varies from 13 percent to 34 percent. Augmented lithogenicity in CD is due to a disruption of the enterohepatic circulation of bile acids owed to gallbladder hypomotility, extensive ileal involvement and/or resection of the small bowel; presenting a 3X increased risk of gallstones development. Both cholesterol and pigment stones can be found in CD.

Drug Induced Pancreatitis

Generally, drug exposure can cause acute pancreatitis in up to two percent of the general population. Azathioprine (AZA) and 6-mercaptopurine (MP), immunosuppressors commonly used to treat IBD, appear to be the most important cause of pancreatitis in CD. Moreover, Crohn’s disease patients hold a higher risk of acute pancreatitis than patients treated with these same drugs for other causes, especially when they are female. A 3.1 percent incidence rate of AP in patients treated with AZA/MP has been described.

Drugs that follow the lead are mesalamine, corticosteroids, and metronidazole. Subsequent causes of AP in IBD have an Idiopathic (20.7 percent) and biliary (12.2 percent) etiology.

Pancreatic Cancer

Pancreatic cancer (PC) is the third leading cause of cancer deaths among men and women in the United States, accounting for 7 percent of all cancer related deaths. IBD patients, especially male with UC, seem to be at an increased risk of developing this condition. This may be due to the repeated episodes of inflammation, although a cause-effect relationship is yet to be established.

UC patients hold a 4.85-fold risk of PC. While IBD men show a 6.22 times higher risk of developing this type of cancer, IBD women do not seem to have an increased risk of pancreatic malignancy, nor do patients with Crohn’s disease. Altogether, IBD patients display a 3.36X higher risk of developing pancreatic carcinoma.

Laboratory findings in pancreatic cancer are frequently nonspecific. However, modern imaging scanning helps diagnose this entity in clinically expressive patients. Imaging modalities include CT, endoscopic ultrasonography (EUS), Magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP).

EUS has a detection rate of 99-100 percent for all pancreatic malignancies, including those smaller than 3 cm. Also, it is as precise as ERCP or MRCP for obstructive jaundice’s etiology identification.

Management

The management of the binomial IBD-AP does not differ from the conventional approach of patients with acute pancreatitis. Drugs with known pancreatic toxicity should be excluded temporarily from treatment and/or replaced with a safer therapeutic alternative. For example, 5-aminosalicylic acid (5-ASA) mesalamine, can be safely switched to 4-aminosalicylic acid (4-ASA), a well-tolerated nontoxic agent for the pancreas.

In active IBD, serum amylase should be assessed weekly as a forecaster of the appearance of AP. Prognosis of AP in IBD beyond the acute critical period is mostly benign. Recurrence rate fluctuates between 13-21 percent; however, AP is a severe disease with an overall mortality of 5 percent. This rate reaches up to 30 percent in necrotizing pancreatitis and infected necrosis.

The use of endoscopic delivered anastomotic stents, formerly only possible through surgery, creates a valuable conduit between two lumens, enabling drainage of large fluid collections and bypass of blockages and strictures. This less invasive procedure is a huge step forward in the management of commonly present complications associated to the IBD-pancreas binomial.

Finally, given inflammatory bowel disease’s chronicity and disease-related complications, efforts to increase patient awareness contribute to medical compliance and improve the management of symptoms. Moreover, since IBD patients are more prone to develop pancreatic cancer after a certain period of time, it must be emphasized to assess for malignancy periodically.

Conclusion

IBD includes Crohn’s disease, ulcerative colitis and microscopic colitis, chronic diseases attributed to immunologic disturbances. Each requires a tailored medical approach. It is evident that pancreatic involvement in IBD is a tangible entity, and not uncommon. Therefore, to improve IBD patients’ quality of life, physicians need to be aware of the onset of pancreatic diseases and be able to treat them appropriately.
References


WE CHOOSE love.
We choose Community Hospice.

More Northeast Florida families choose Community Hospice—one of only 39 hospices in the nation and the only Florida hospice to achieve Hospice Honors “Elite Status” for 2015, our second year in a row. This prestigious award recognizes hospices providing the highest levels of family satisfaction.* For 36 years, we’ve helped families honor the choices that matter most. When the time is right for your patients, ask for Community Hospice.

*Based on Family Evaluation of Hospice Care survey results for each quarter of 2012 – 2014.

Call 904.407.6500 or visit CommunityHospice.com to request care.
Nova Southeastern University is Florida's largest private, not-for-profit institution of higher education, and it houses the only physician assistant (PA) program in Jacksonville. We invite you to help our students realize their potential by sharing your knowledge with them while enjoying access to NSU's library of resources—including online journals, medical references, medical information portals, and Continuing Medical Education for qualified preceptors. Work with our students and inspire them to be tomorrow's leaders in health care.

Clinical preceptors are key to our student's success. Become an inspiration by mentoring an NSU physician assistant student today! For more information, call (904) 245-8990 or visit www.nova.edu/pa/Jacksonville.