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Crohn's Disease: Management, Emerging Therapies and the Role of the Pharmacist

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Abstract

Crohn's disease is a relapsing-remitting disorder of the gastrointestinal tract caused by a mixture of genetic and environmental factors. Pharmacologic treatment of Crohn's disease is patient-specific, and regimens vary widely between individuals. Drug regimens are typically based on 5-aminosalicylate therapy and may include a combination of steroids, histamine 2 receptor antagonists, proton pump inhibitors, immunomodulators, antibiotics, biologic agents and other medications aimed at symptom relief. A new medication, vedolizumab, is currently in phase III clinical trials awaiting U.S. Food and Drug Administration (FDA) approval for use in Crohn's disease. Vedolizumab is an alpha-integrin inhibitor, which is anticipated to have a better safety profile than Tysabri® (natalizumab), an alpha-integrin inhibitor already approved for treatment of Crohn's disease. Pharmacists have an opportunity to educate Crohn's disease patients about nonpharmacologic management including counseling on diet, exercise, stress-relief therapy and use of multivitamins as well as the importance of regular colonoscopies and visits to a primary care practitioner. Pharmacists can also educate patients and practitioners about alternative therapies including probiotics, fecal microbiota transplantation and fish oils which may help manage the disease.

Introduction

Crohn's disease is an inflammatory bowel disease (IBD), which can negatively affect the lives of many patients. While there are both pharmacologic and nonpharmacologic steps all patients can take to suppress the disease and its complications, treatment is highly individualized. Many patients will often not respond to initial therapy or may lose responsiveness over time. The need for new medications to combat Crohn's disease is highly recognized. Vedolizumab has completed phase III clinical trials and is awaiting FDA approval. Its safety and efficacy in these trials are encouraging for potential use in Crohn's disease patients. Pharmacists can play a large role in the management of these patients, as they will be instrumental in monitoring complex drug therapies, ensuring appropriate laboratory testing, and educating patients on diet, other nonpharmacologic treatments, and new investigational therapies. Pharmacists have the opportunity to make a difference in improving the quality of life of Crohn's disease patients in multiple settings, which include community, institutional, specialty pharmacy and primary care practice.

Background of Disease and Traditional Therapy

Crohn's disease is an increasingly prevalent idiopathic form of IBD. Since it affects all ages and ethnicities, as well as both men and women, Crohn's disease plays a significant role in the lives of approximately 6 million Americans.[1] The chronic, relapsing autoimmune inflammatory nature of this disease typically presents as a discontinuation of the mucosa of the gastrointestinal tract (GIT) and may result in complications such as strictures, fistulas, lesions, obstructions or abscesses. Lesions of the intestine are oftentimes irreversible. While the mucosa of the entire GIT from the mouth to the anus can be affected, the majority of cases are located in the terminal ileum and colon. Clinical implications include diarrhea or constipation, fever, abdominal pain, passage of mucus and blood in the stool, signs of bowel obstruction, mouth sores and clubbing of the fingernails.[2,3] Diarrhea, as demonstrated by an increase in frequency and decrease in consistency of stool, is the most common clinical implication. Abdominal pain, another common symptom, is typically seen in the right lower quadrant and is exacerbated by eating.[3] As a result of this exacerbation with food, weight loss is a frequent occurrence in Crohn's disease.[4]

Crohn's disease is not a reportable condition in the United States, which limits the ability to determine which populations are at highest risk. Data is also skewed by the difficulty in differentiating Crohn's disease from a similar form of IBD known as ulcerative colitis. Researchers have conducted multiple studies to determine the populations that have the highest incidence of Crohn's disease. Crohn's disease may occur at any age, but most cases are diagnosed in early adulthood with a large peak in adults 20 to 30 years old. A second peak of incidence occurs in adults 50 to 60 years old.[1,5] About 25 percent of IBD diagnoses occur during childhood and, unfortunately, pediatric patients generally present with a more severe form.[5] Pediatric cases of Crohn's disease occur more often in boys than girls, but in adults more cases occur in women than men. Data indicate more cases of Crohn's disease in the Northeast and Midwest regions of the United States when compared to the Southern and Western regions.[1] Historically, Crohn's disease is most common in Caucasians, with a genetic-based increase in prevalence among individuals of Eastern European (Ashkenazi) Jewish descent.[6] However, recent studies have shown an increase in the rate of African-Americans presenting with Crohn's disease, and the rate of Crohn's-induced hospitalizations of African-Americans is now similar to Caucasians. Incidence in Asian-Americans and Hispanic-Americans is significantly lower compared to Caucasians and African-Americans.[7]

The exact cause of Crohn's disease is unknown, but the disease seems to be influenced by both genetics and environmental factors. Genome-wide association studies have shown genetic variance to be the major contributor to about 23 percent of cases. These genetic variants have been shown to alter the regulation and efficiency of key molecular pathways

in the body such as microbial defense, innate immune responses, autophagy, reactive oxygen species generation, and lymphocyte differentiation.[8] Due to altered regulation, the GIT is more prone to chronic injury and infection. Although microorganisms such as Escherichia coli, Salmonella spp. and Campylobacter spp. have been hypothesized to trigger the onset of Crohn's disease, researchers have not been able to pinpoint one specific microorganism as the causative agent.[9] These harmful microorganisms can adhere to epithelial cells of the intestine, replicate and stimulate an immune response, which induces epithelial cell injury, causing inflammation and discontinuation of the intestinal mucosa. Crohn's disease patients are also commonly postulated to have a "leaky gut" in which intestinal permeability is increased, resulting in intestinal substances leaking out into the bloodstream. Moreover, most Crohn's disease patients have altered bowel flora, which leaves the GIT unable to defend against the activity of harmful microorganisms.[3,8]

Many factors contribute to an increase in harmful microorganisms in the intestinal mucosa. For example, the consumption of refined sugars and preservatives present in many foods in the United States and other industrialized areas favor growth of detrimental bacteria in the intestine. As a result, diet can be a key component in the management of Crohn's disease. Children growing up in areas with poor sanitation are exposed to an increased repertoire of pathogens and infections, and thus, develop a more robust immune system. Therefore, these children may be protected against agents which may induce Crohn's disease, resulting in lower prevalence in children in areas of poor hygiene compared to children who grow up with increased sanitation and less pathogen exposure in industrialized areas. This idea is known as the hygiene hypothesis and is theorized as a contributor to the development of IBD.[10] Drug-induced Crohn's disease is also possible. Chronic use of antibiotics can kill protective bacteria in the intestine leaving the epithelial cells more prone to injury by harmful microorganisms. Other risk factors for developing Crohn's disease include cigarette smoking and use of oral contraceptives.[7]

Currently, no definitive diagnostic test exists for Crohn's disease. Analysis of symptoms and clinical laboratory values as well as endoscopic, histologic, and radiologic examination criteria lead to confirmation of the disease.[2,4] There is no gold standard when it comes to treating Crohn's disease. There are several different treatment guidelines available, including those from the American Academy of Family Physicians (AAFP), the American College of Gastroenterology (ACG), and the American Gastroenterological Association (AGA). However, the guidelines do not agree on a strong first-line recommendation. Therefore, optimal first-line therapy is patient-specific and dependent on the location, severity and any complications of the disease that are present. The two primary goals of therapy are to treat acute flare-ups of symptoms and maintain remission. Other goals of therapy are limiting exposure to corticosteroids, minimizing adverse effects of therapy, decreasing hospitalizations and improving patients' quality of life.

Five classes of drugs affecting the small and large intestine are typically utilized for Crohn's disease: 5-aminosalicylates, immunomodulators, antibiotics, corticosteroids and biologics. For mild to moderate disease, 5-aminosalicylates such as mesalamine, sulfasalazine, olsalazine and balsalazide are most commonly used as first-line therapy to achieve remission. Topical mesalamine in the form of suppositories or enemas can be effective in treating distal Crohn's disease and maintaining remission in mild to moderate patients. Immunomodulators such as azathioprine, mercaptopurine (6-MP), and methotrexate (MTX) are useful in maintaining remission when 5-aminosalicylates fail, in steroid-dependent disease and in fistulizing disease. The use of the immunomodulator cyclosporine is limited to cases of severe disease in which other treatments have failed, due to its risk of serious side effects. It is typically administered intravenously as a last ditch effort to a hospitalized patient in an effort to prevent or delay surgery. Antibiotics, including ciprofloxacin and metronidazole, can be used to treat fistulizing disease and flare-ups, while also playing a role in achieving remission in mild to moderate disease when 5-aminosalicylates are not sufficient. Corticosteroids such as prednisone can be used to treat acute flares and to induce remission in moderate to severe disease, but should never be used long-term to maintain remission since it has a high incidence of serious side effects including infection, osteoporosis, adrenal insufficiency, glaucoma, muscle wasting, fat redistribution and hypertension. Corticosteroids should be tapered down slowly and as early as possible in order to avoid these serious complications. Biologics are typically reserved for fistulizing disease or severe disease refractory to other medication classes. Biologics are commonly used as an alternative to immunomodulators or occasionally in combination with immunomodulators, although combination of these two classes is highly debated.[11] Biologics include tumor necrosis factor alpha (TNF-α) inhibitors adalimumab, infliximab, and certolizumab pegol, as well as the alpha-4 integrin inhibitor, natalizumab.

New Drug Therapy: Vedolizumab

Patients with moderate to severe Crohn's disease have often tried and failed many medications including TNF-α inhibitors such as adalimumab, infliximab and certolizumab pegol. There is an unmet need for new therapies to treat patients with severe disease. A new class of medications, known as alpha-4 integrin inhibitors, has been developed for this purpose. This class includes the medication natalizumab (Tysabri®), which is FDA approved for Crohn's disease. Integrin inhibitors act to prevent leukocyte extravasation (crossing the endothelium of blood vessels) into the mucosa of the GIT, which decreases the inflammatory response in patients who have an upregulated, dysfunctional immune system.[12] Extravasation of leukocytes involves the coordinated efforts of leukocytes and vascular endothelial cells. Integrins on the surfaces of leukocytes bind to receptors on endothelial cells and activate intracellular signaling. The extravasation process involves multiple steps including tethering, rolling, activation, adhesion, extravasation and migration as the leukocytes enter the GIT.[12,13] In Crohn's disease, it is the T-cells expressing α4β7 integrin, which exclusively bind to endothelium in the GIT and lymphoid tissue.[12] The α4β7

integrin binds to mucosal addressin-cell adhesion molecule-1 (MAdCAM-1), which is a receptor only expressed on the vasculature of the GIT.[12,14] MAdCAM-1 increases T-cell deposition in the GIT and is a major contributor to inflammation in this region. Natalizumab was developed as a monoclonal antibody, which binds to the α4 integrin monomer, resulting in binding both α4 integrin heterodimers on T cells, α4β7 and α4β1, to block their respective attachments to the vascular cell adhesion molecule-1 (VCAM-1) and MAdCAM-1. Binding to α4β7 and α4β1 prevents integrin association with the endothelial receptors and reduces extravasation of inflammatory cells. Natalizumab has been used successfully for treatment in Crohn's disease, ulcerative colitis and multiple sclerosis.[12] While it has displayed efficacy in multiple diseases, natalizumab has a major drawback of causing a serious and often fatal disease known as progressive multifocal leukoencephalopathy (PML) caused by the John Cunningham (JC) virus.[12] Natalizumab was withdrawn from the market by the FDA and reintroduced in 2006 with a specialized Risk Evaluation and Mitigation Strategy (REMS) safety prescribing program.[12] The reason for this effect with natalizumab is prevention of α4β1 integrin from binding to VCAM-1, which is thought to negatively affect immunity in the central nervous system and increase the risk for development of PML.

Vedolizumab, a humanized version of a mouse antibody, selectively binds the α4β7 integrin.[12,13] Vedolizumab is a smaller molecule than natalizumab allowing it to selectively target GIT integrins. Also, vedolizumab does not affect binding to VCAM-1 and has not yet been associated with development of PML.[12,14] Like natalizumab, vedolizumab is administered intravenously. Vedolizumab has completed phase III clinical trials and is awaiting FDA approval to be brought to market.[12]

A phase III randomized, parallel-group, placebo-controlled, double-blinded study conducted from December 2008 to May 2012 evaluated the safety and efficacy of vedolizumab as induction and maintenance therapy for Crohn's disease. Inclusion criteria included patients 18 to 80 years old with at least a three month history of Crohn's disease with a Crohn's Disease Activity Index (CDAI) of 220 to 450 (CDAI scores range from 0 to 600 with higher scores pointing to greater disease activity). Patients also had to have other gastrointestinal markers of certain severity including: C-reactive protein, colonoscopy findings or fecal calprotectin. Patients had to be unresponsive or previously display unacceptable side effects with glucocorticoid therapy, immunosuppressive agents, or TNF-α inhibitors. Exclusion criteria encompass patients with severe disease complications such as stoma, extensive small-bowel or colon resections, strictures, abdominal abscesses, cancer and tuberculosis. Patients were screened using physical exams, neurologic exams and questionnaires, including one to classify symptoms of PML as well as the Inflammatory Bowel Disease Questionnaire.[15]

The trial investigated both induction and maintenance treatment using vedolizumab. For the induction component, patients were randomized to receive placebo or vedolizumab 300 mg at weeks 0 and 2 and were assessed for disease status through week 6. A second open-label cohort received the same regimen of vedolizumab as the previously mentioned group receiving induction therapy. This group of patients was included in the study to meet sample size requirements for the maintenance phase of the trial. Patients eligible for the maintenance phase of the study were patients from both cohorts who displayed a clinical response to vedolizumab at week 6. Participants were randomized in a 1:1:1 fashion to vedolizumab dosed every four weeks, every eight weeks or placebo (frequency not specified) for 52 weeks. Patients who did not achieve a clinical response to vedolizumab by week 6 of induction therapy continued to receive vedolizumab 300 mg every four weeks for 52 weeks. Patients in the placebo group during the induction phase remained in the placebo group for the maintenance phase.[15]

Primary end points for the induction trial were clinical remission defined by a CDAI less than or equal to 150 and a CDAI-100 response, defined as a 100 point CDAI score reduction. The secondary end point was the change in C-reactive protein from baseline to 6 weeks. Statistical significance for the entire trial was set at 5 percent (alpha=0.05). Results showed 14.5 percent of patients receiving vedolizumab and 6.8 percent of patients receiving placebo reached clinical remission by week 6 ($p=0.02$). Of those receiving vedolizumab and placebo, 31.4 percent and 25.7 percent, respectively, had a CDAI-100 response ($p=0.23$). Changes in C-reactive protein were similar across both groups.[15]

The primary end point for the maintenance trial was clinical remission at week 52 and the secondary end points were CDAI-100 response at week 52, remission at week 52 without the use of glucocorticoids, and clinical remission at greater than or equal to 80 percent of all study visits including the final visit at week 52. Results showed 36.4 percent of patients receiving vedolizumab every four weeks and 39 percent of patients receiving vedolizumab every eight weeks were in clinical remission at week 52. Only 21.6 percent of patients in the placebo group reached clinical remission, producing comparison p-values of $p=0.004$ and $p<0.001$ for the four-week and eight-week vedolizumab groups compared to placebo, respectively. Vedolizumab groups also showed a trend towards greater proportions of patients with a CDAI-100 response and glucocorticoid-free remission than with placebo; however, the differences in clinical remission were not significant.[15]

This trial displayed moderate effects on induction and maintenance of clinical remission in patients with moderate to severe Crohn's disease who received vedolizumab therapy. Patients enrolled in the study had refractory disease and approximately 50 percent of patients had prior treatment failure to other medications, including TNF-α inhibitors. Further trials are necessary to determine which patients may benefit most from vedolizumab therapy. Once it comes to market, vedolizumab will likely be a safer choice than natalizumab for Crohn's disease due to a lower incidence of PML.[15]

On Dec. 9, 2013, a joint meeting of the FDA's Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk

Management Advisory Committee recommended vedolizumab for use in Crohn's disease as well as ulcerative colitis. Specific recommendations for vedolizumab therapy in Crohn's disease included use in patients who failed TNF-α inhibitors or conventional therapy to reduce signs and symptoms, to achieve clinical remission or glucocorticoid-free remission and to stimulate mucosal healing in moderate to severe Crohn's disease. The committee reached unanimous agreement that Takeda Pharmaceuticals appropriately characterized the low risk of PML with vedolizumab therapy to support approval.[16] Although the committee has shown support, vedolizumab still needs FDA approval. The FDA has set a Prescription Drug User Fee Act (PDUFA) Priority Review action date for the indication of vedolizumab in ulcerative colitis as May 20, 2014. This date is a target for the FDA to make a final decision on approval. A PDUFA standard review action date for indication in Crohn's disease has been made for June 18, 2014.[17] If approved, vedolizumab will enter the market under the brand name Entyvio®.

Nonpharmacologic Treatment

Along with standard pharmacologic treatments, nonpharmacologic treatments have proven beneficial for Crohn's disease patients. Lifestyle modifications such as dietary changes and symptomatic or supportive treatment are important. Maintaining a well-balanced diet promotes healing and relieves symptoms in many patients suffering from Crohn's disease. Good nutrition helps compensate for nutritional losses due to Crohn's disease. Dietary suggestions are different depending on whether the patient is in a period of active or inactive disease. When the disease state is inactive, patients should stay hydrated and consume low fiber carbohydrates like legumes, oat bran, and barley, proteins such as lean meats and eggs, healthy fats like olive oil, fruits, and vegetables. When a patient's disease is active, health care professionals can recommend applesauce, bananas, bland foods, soft foods, plain cereals, proteins as accepted, and small, frequent meals.[18] Patients with active disease should also be educated to avoid high fiber foods, high fat foods, nuts, seeds, popcorn, gluten, caffeine, alcohol, raw fruits, raw vegetables, dairy, spicy foods, and larger portions. However, all dietary recommendations remain patient specific. Each patient may also possess his or her own specific trigger food, which should be avoided, because it may cause flares of symptoms and decreased quality of life. Patients should be advised to keep a food diary, which should include all foods eaten each day as well as Crohn's disease symptoms such as abdominal pain, a description of bowel habits and overall well-being. This process helps identify triggers, encourages patients to eat well-balanced foods and allows positive dietary habits to be observed. Overall, Crohn's disease manifests differently between individuals; therefore, it is best to individualize each patient's diet to alleviate symptoms.

Maintaining a healthy diet is important, but there are other nonpharmacologic therapies that may help reduce flare-ups and prevent symptoms. First, those suffering with Crohn's disease should stop smoking as this worsens symptoms and can decrease responsiveness to certain treatments.[19] Also, stress relief and general health maintenance are beneficial in providing symptomatic relief and preventing exacerbations. Options for stress relief include relaxation, breathing exercises, meditation, acupuncture, reading books and other relaxing activities.[20] Implementing low-intensity exercise for 30 minutes three times per week aids in diminishing depression, which often accompanies Crohn's disease.[21]

Numerous other complementary alternative medicines are available. These are believed to be safe, but may require additional studies to elucidate efficacy in the treatment of Crohn's disease. These options include probiotics, fecal microbiota transplantation and fish oils. Probiotics are living microbial food ingredients, which beneficially alter the intestinal flora in an unknown mechanism. Although studies regarding probiotics in Crohn's disease have resulted in mixed conclusions on efficacy, the use of VSL#3 specifically may help patients achieve remission. VSL#3 is a mixture of eight different strands of bacteria, which influence the immune response by several mechanisms.[23] Fecal microbiota transplantation represents an alternative therapy to use when standard treatments have failed. This process involves transferring a safe, donated stool into the patient via an enema or nasogastric tube in order to replenish and balance bacteria in the colon.[24] Fish oils and omega-3 fatty acids may have positive anti-inflammatory effects in the intestines.[22] Even though all of these options are still under investigation, they may be good options for the treatment of Crohn's disease.

After medications and nonpharmacologic treatments fail as treatment for Crohn's disease, surgery is the final option. According to the National Cooperative Crohn's Disease Study, the probability of requiring surgery is 78 percent after 20 years of Crohn's disease symptoms, and the probability jumps to 90 percent after 30 years of symptoms.[25] Possible procedures include strictureplasty, resection, colectomy, removal of abscesses (pus-filled sacs) and correction of abnormal tracts or fistulas.[26] However, surgery is not curative and is a last-ditch effort for treating Crohn's disease.

The Pharmacist's Role

As health care providers, pharmacists must be educated in Crohn's disease pharmacologic and nonpharmacologic treatments as well as appropriate patient counseling and recommendation points. Pharmacists should highlight the importance of avoiding non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen due to bleeding risk. Within one week of therapy with NSAIDs, approximately 25 percent of patients have flares.[19] Many Crohn's disease patients experience deficiencies in folate and vitamin B12. Vitamin B12 deficiency is especially prevalent when the ileum is affected since this is the primary site of absorption of vitamin B12. Therefore, pharmacists should recommend frequent screenings and supplementation. Since sulfasalazine and methotrexate impair folate metabolism, patients taking these medications require more folic acid than patients not on these therapies.[27] Vitamin D and calcium may also be depleted in Crohn's disease patients due to impaired absorption putting patients at increased risk for osteoporosis.[28] Vitamins and supplements should be taken during both the active and inactive phases of the disease to

replenish deficiencies.[22] Another counseling point to emphasize is the necessity for periodic colonoscopies in which the frequency is determined by disease severity, duration and personal or family history of colorectal cancer. The risk of acquiring colorectal cancer significantly increases eight to 10 years after development of Crohn's disease, and at that point, patients may require regular colonoscopies every one to two years.[29] It is important to ensure that patients keep a list of any supplements, over-the-counter or prescription medications they take in order to keep their doctors, pharmacists and other health care professionals informed. Pharmacists should also counsel patients on nonpharmacologic treatments, including foods and drinks to avoid and those that may be better options. As the most accessible health care provider, it is important for pharmacists to remain knowledgeable and up-to-date on new treatments, recommendations and counseling points to benefit patients suffering from Crohn's disease.

Conclusion

Crohn's disease patients may feel overwhelmed or burdened by their disease state and the complexity of their medication regimens. When experiencing a disease flare, the quality of life of a Crohn's disease patient is negatively affected. Pharmacists play a large role in helping these patients to better manage their medications and can provide great insight into the various pharmacologic and nonpharmacologic therapies available for treatment of Crohn's disease.

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