



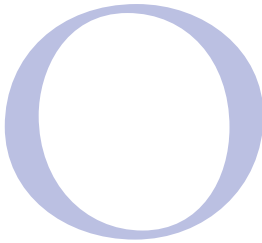
Crohn's Disease and Ulcerative Colitis:
Medications



CROHN'S
&
COLITIS
FOUNDATION
OF AMERICA

The Crohn's & Colitis Foundation of America is a non-profit, volunteer driven organization dedicated to finding the cure for Crohn's disease and ulcerative colitis. CCFA sponsors basic and clinical research of the highest quality. The foundation also offers a wide range of educational programs for patients and healthcare professionals, and provides supportive services to help people cope with these chronic intestinal diseases. CCFA programs are supported solely by contributions from the public.

We hope that this brochure will help you to better understand these illnesses, and to become an active member of your healthcare team.



f the many exciting recent developments in inflammatory bowel diseases (IBD), medical therapies have received the most attention and funding. Before 1990, only a few medications were available: corticosteroids, sulfasalazine, metronidazole, azathioprine, and 6-mercaptopurine (6-MP). Since then, there has been a dramatic increase, both in research and in medications to treat Crohn's disease and ulcerative colitis. As a result, people with IBD have more treatment options than ever before. What's more, we can expect that a growing number of new therapies will become available in the years ahead.

Medical therapy for IBD has three main goals: inducing remission (controlling flare-ups of the disease), maintaining remission (preventing flare-ups), and improving the patient's quality of life. To achieve these goals, therapy must suppress the chronic inflammation in the intestine, which causes the symptoms of

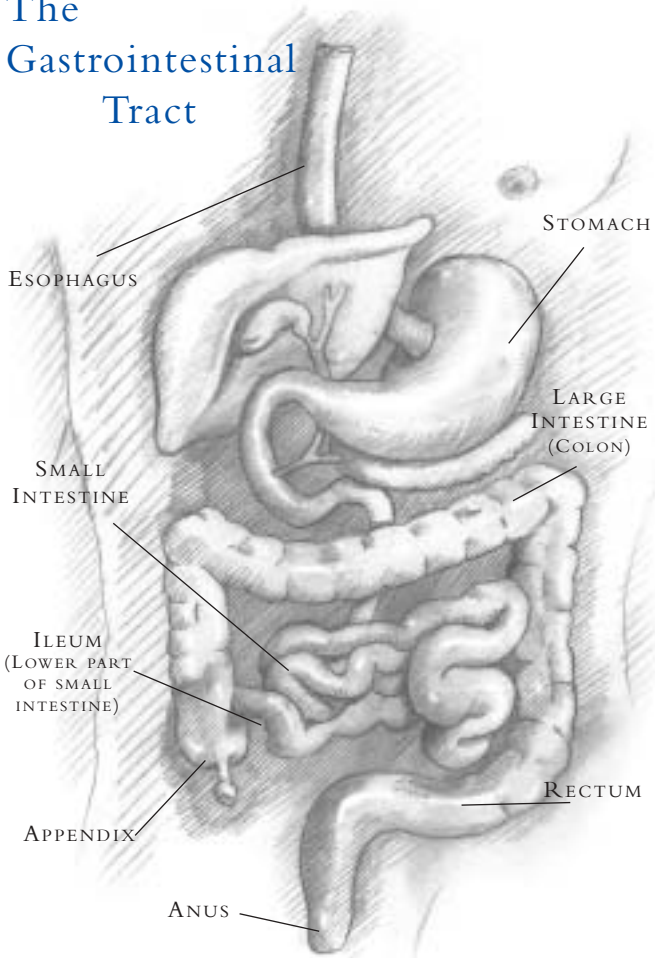
IBD. When this inflammation is under control, patients can get the nutrients they need, and avoid surgery and long-term complications. (Other brochures in this series deal specifically with these issues. For a complete list, please see the inside back cover of this booklet.)

The ideal medication would be effective, safe (have few side effects), simple to administer, and affordable. But there is no single ideal therapy for IBD. As the following overview shows, treatments must be tailored to each person's needs. A number of factors will determine which treatments are appropriate for you, including which part of your intestine is affected, the severity of your symptoms, and whether you are able to take certain drugs without experiencing side effects. It's also important to keep in mind that your therapeutic needs may change as time goes by. Clearly, it is important that you and your physician thoroughly discuss the best course of therapy for you.

AMINOSALICYLATES

Aminosalicylates were the first class of drug that was shown to be beneficial in IBD. The first aminosalicylate to be widely used was sulfasalazine (Azulfidine®). To make this drug, a substance called sulfapyridine is bonded to an aspirin-like compound known as 5-aminosalicylate (5-ASA). 5-ASA, which has anti-inflammatory properties, is the active portion of the

The Gastrointestinal Tract



drug. The sulfapyridine portion carries 5-ASA to the intestine. It is responsible for most of the drug's side effects (headache, nausea, etc).

To reduce these side effects, researchers developed newer oral drugs that can deliver the 5-ASA molecule without the sulfapyridine carrier. Examples are olsalazine (Dipentum[®]), mesalamine (Asacol[®], Canasa[®], Pentasa[®] and Rowasa[®]), and balsalazide (Colazal[®]). Up to 90 percent of people who cannot tolerate sulfasalazine are able to take other mesalamine products.

There are several ways to deliver 5-ASA to the bowel:

- Enema formulations (Rowasa[®]) allow mesalamine to be applied directly to the left colon (up to the splenic flexure, a bend in the colon near the spleen). Suppositories (Canasa[®]) allow direct application from the rectum up to the sigmoid colon (the lower part of the large intestine, which is connected to the rectum).
- Oral, delayed-release preparations can deliver 5-ASA directly to the small intestine and colon (e.g., Pentasa) or to the ileum (the lower part of the small intestine) and/or the colon (e.g., Asacol, Colazal). This ensures that 5-ASA will be active where inflammation is located.

In people with mild to moderately active ulcerative colitis, sulfasalazine is as effective as the mesalamine products, when it is used in equal doses. But most studies have shown that the newer 5-ASAs have significantly fewer side effects than sulfasalazine. The dose of oral aminosalicylates needed to *achieve* remission is typically the same dose needed to *maintain* remission. The use of any of the

aminosalicylates, including sulfasalazine, for severely active ulcerative colitis has not been adequately tested.

Topical mesalamine (Rowasa enemas) is effective in mild to moderate colitis that affects only the left side of the colon. Clinical responses (positive results) occur in up to 80 percent of patients who use these therapies once a day. A similar proportion of ulcerative proctitis patients (people whose disease is limited to the rectum and the beginning of the colon) will respond to mesalamine suppositories. These are usually dosed twice daily. A combination of mesalamine enemas and pills can be more effective than pills alone. Remission has been maintained with mesalamine suppositories in people with proctitis, or with enemas in people with left-sided colitis.

The data from clinical research are less clear for the use of aminosalicylates in Crohn's disease, but most physicians have found these drugs helpful. Early trials did not demonstrate that aminosalicylates achieved remission in people with active Crohn's. But two recent trials showed that a higher dose (four grams of Pentasa, and 3.2 grams of Asacol) were beneficial. This suggests that high doses are needed for effectiveness. Similarly, mesalamine pills have been shown to maintain remission in Crohn's. This beneficial effect is most marked in patients who have recently undergone surgery. Mesalamine delayed or prevented the disease from recurring after bowel resection. To perform this operation, the surgeon removes the diseased portion of intestine, then reconnects the ends of the remaining intestine. Sulfasalazine is effective when Crohn's disease is limited to the colon.

CORTICOSTEROIDS

Corticosteroids (prednisone, Medrol®, methylprednisolone, hydrocortisone, etc.) have been the mainstay of treatment for acute flare-ups since these drugs were first used for IBD in the 1950s. In mild to moderately active disease, steroid pills are usually effective. In severe IBD, intravenously administered steroids are often necessary. Rectally administered steroids (enemas, suppositories, or foams) are helpful to people with left-sided colitis. They also may be used, with other therapies, in people with more widespread disease that begins at the rectum.

Twenty to 30 percent of patients with acute (active) ulcerative colitis or Crohn's will not respond to corticosteroids (regardless of dose or route of administration). In addition, 30–40 percent of patients have steroid-dependent disease: They are unable to taper off steroids without experiencing flare-ups of IBD. (Because these drugs affect the body's hormone balance, dosage cannot be stopped abruptly. Steroid use must be tapered off gradually or serious side effects can occur.) Based on data from controlled trials, which compare the study drug to another medication or to a placebo (a harmless substance), steroids have not been beneficial for maintaining remission in either disease and should not be used long-term.

The anti-inflammatory benefits of steroids often are counterbalanced by their disfiguring side effects. For example, osteoporosis (bone loss), cataracts, stretch marks, weight gain, diabetes, hypertension and psychiatric symptoms frequently occur after long-term use. Thus, physicians often choose safer medications (e.g., mesalamine products, antibiotics) as initial therapy.

Physicians use several strategies to reduce the risk of developing side effects: tapering off steroids rapidly, yet carefully; every-other-day dosing; rectally applied corticosteroids (enemas, foam, or suppositories); and rapidly metabolized corticosteroids such as budesonide (Entocort™EC) which is described below. To help prevent osteoporosis, many physicians routinely prescribe multivitamins (containing vitamin D) and calcium supplements. Hormone replacement therapy also has been shown to be effective in preventing osteoporosis in women with IBD. Bisphosphonates, compounds that have been shown to inhibit bone loss, have not yet been fully tested in IBD patients on steroids, but are effective in other diseases that require long-term steroid therapy.

To date, budesonide (Entocort EC), the best-evaluated of the rapidly metabolized corticosteroids, is the only drug of this kind to be approved by the FDA for the treatment of Crohn's disease. This type of steroid is quickly cleared from the blood stream, thus reducing most side effects. Specially formulated budesonide pills release the drug in the ileum and the colon. This therapy has been shown to be effective in treating active Crohn's that involves these areas. Recent data have shown budesonide to be as effective as traditional steroids, with significantly fewer side effects. It should be noted, however, that studies have not determined that budesonide is effective for long-term use, and the potential long-term effects (such as osteoporosis and other corticosteroid-related side effects) are not yet known.

ANTIBIOTICS

Antibiotics are used as a primary therapy for IBD, even though researchers have not

identified any infectious cause of these illnesses. Researchers believe that antibiotics control IBD by reducing the intestinal bacteria and by directly suppressing the intestine's immune system.

Metronidazole (Flagyl®) is the most extensively studied antibiotic. As a primary therapy for active Crohn's, this drug has been shown to be superior to placebo and equal to sulfasalazine, especially when the illness affects the colon.

Metronidazole also may delay the recurrence of Crohn's for the first two to three years after a person undergoes a resection of the ileum. In more than 50 percent of individuals treated, metronidazole can be effective in managing perineal Crohn's (disease involving the pelvic area). The drug's effectiveness for maintaining remission in Crohn's has yet to be rigorously tested in large, placebo-controlled trials.

Metronidazole has not been shown to be beneficial in active ulcerative colitis, and has no role in maintaining remission in ulcerative colitis.

Adverse reactions to metronidazole may include nausea, headache, and loss of appetite. Because this drug can affect the breakdown of alcohol, it is best if patients avoid alcoholic beverages while on metronidazole.

Large trials have failed to demonstrate that antibiotics have value in treating severe ulcerative colitis. However, before considering a severely ill patient to be unresponsive to all medical therapy, a physician may prescribe broad-spectrum antibiotics (i.e., those that fight a wide range of bacteria). This therapy is sometimes beneficial in such cases. Metronidazole also has been proven effective in people who develop "pouchitis" after ileoanal anastomosis

surgery is performed. This surgery is an ostomy alternative, in which an internal pouch is formed from the patient's ileum, eliminating the need to wear an external appliance. The pouch sometimes becomes severely inflamed—hence the term “pouchitis.”

Ciprofloxacin (Cipro[®]) is a second antibiotic that is commonly used to treat active Crohn's, improve anal symptoms, and heal fistulas (abnormal channels between two loops of intestine, or between the intestine and another structure, such as the skin).

IMMUNOMODULATORS

The use of immunosuppressant agents, such as azathioprine (Imuran[®]) and 6-mercaptopurine (6-MP, Purinethol[®]), has emerged as a tool in treating both active and inactive IBD. As their name implies, these drugs block the activation of the immune system, which plays a key role in causing the inflammatory symptoms of IBD. Azathioprine and 6-MP have been used to treat patients with active Crohn's since the 1960s. These drugs are considered appropriate for people who:

- have disease that does not respond to treatment with aminosalicylates, antibiotics, or corticosteroids;
- have steroid-dependent disease;
- have experienced side effects with corticosteroid treatment;
- have perineal disease that does not respond to antibiotics;
- have fistulas;
- need to maintain remission.

Most studies suggest that these agents are significantly more effective than placebo for active Crohn's disease. The use of these drugs, however, is limited by their slow

onset of action (three to six months for full effect). Azathioprine and 6-MP are taken orally; intravenous administration does not speed up their effectiveness. These drugs also have reduced relapses in Crohn's patients who are in remission. The role of azathioprine and 6-MP in ulcerative colitis is emerging. Their slow onset of action usually dictates that they be combined with a second drug (such as corticosteroids). Nevertheless, these medications have proven to be superior to placebo for active colitis in controlled trials. One controlled study has examined the use of azathioprine for maintaining remission in colitis; this also demonstrated significant benefit. Because azathioprine and 6-MP have fewer side effects than corticosteroids, they are particularly useful in sparing IBD patients from steroid use. A recent CCFA-sponsored study showed that, when compared to placebo pills, the use of Pentasa or 6-MP reduced the rate of recurrence of Crohn's disease in patients who had undergone surgical resection of the small bowel.

Azathioprine and 6-MP have lower long-term toxicity than corticosteroids. Approximately 10 percent of patients cannot tolerate these drugs. Side effects can include allergic-type reactions, bone marrow toxicity, infections, inflammation of the pancreas, inflammation of the liver (rare), and lymphoma (very rare, and it is unclear if this is related to medication use). Suppression of the bone marrow can lead to abnormally low levels of the various types of blood cells that the marrow produces. Therefore, regular monitoring of blood counts is recommended during treatment. There are some physicians who advocate using 6-MP or azathioprine at doses that purposely lower the white blood cell count to below-normal levels.

Further testing is needed to determine if this truly is a more effective approach.

Cyclosporine A (Sandimmune[®], Neoral[®]) is an immunosuppressant that has been extensively used in organ transplantation. Recently, it has been used to treat IBD. Cyclosporine has the advantage of a more rapid onset of action (one to two weeks) than azathioprine and 6-MP (three to six months). This drug is effective in patients with active Crohn's disease (who are also receiving steroids), but only when given at high doses. Cyclosporine also has been given to people whose fistulas failed to close when they were taking other medications. Although the fistulas closed in a number of these patients, most reopened when the cyclosporine was stopped. Fewer than one-third of the fistulas remained closed, even if 6-MP or azathioprine were administered.

Cyclosporine has been more successful in treating severe ulcerative colitis. Eighty percent of patients who were hospitalized for severe ulcerative colitis, and who faced surgery despite high doses of intravenous steroids, responded to intravenous cyclosporine. Early reports indicated that as many as 70 percent of these people would require surgery within one to two years anyway after a six-month course of cyclosporine alone. But more recent data suggest that the majority will avoid surgery and stay in remission with the use of 6-MP or azathioprine. This suggests that cyclosporine A can be used in two ways in ulcerative colitis: as a "bridge" to curative elective surgery, which can be performed when the patient is well enough to undergo the procedure; or to control the disease until other immunomodulators, such as 6-MP, have enough time to begin working.

Finally, cyclosporine's benefits must be balanced against its numerous potential serious side effects. These include kidney damage, inflammation of the liver, high blood pressure, seizures, increased susceptibility to infections, and increased risk of lymphomas. As a result, cyclosporine is reserved for seriously ill patients or for fistulas that have not improved with the other therapies.

Methotrexate is a medication that has been used to effectively treat rheumatoid arthritis and psoriasis. Due to this success, an open trial was conducted in 14 Crohn's patients and seven ulcerative colitis patients who had not responded to other medical therapies. More than 70 percent of the patients improved. Although none of the colitis patients achieved remission, more than one-third of the Crohn's patients did.

Methotrexate may work more rapidly than azathioprine and 6-MP, which can require three to six months before symptoms lessen. In this study, most Crohn's patients who responded to the drug improved markedly by eight to 10 weeks. In a larger, placebo-controlled trial, people with chronically active Crohn's received weekly methotrexate injections. Corticosteroids could be reduced or eliminated while inducing remission in these patients. But long-term trials are still needed to evaluate effectiveness. Methotrexate pills have not been as effective as injections.

Methotrexate in any form is not effective in ulcerative colitis.

Toxicity is an important issue that limits methotrexate use in many patients. Side effects are most commonly "flu-like symptoms": nausea, vomiting, fatigue and diarrhea. However, serious side effects involving the bone marrow, liver, and,

rarely, the lungs also have been reported. Methotrexate causes fetal death and congenital abnormalities. Thus, if either partner is receiving methotrexate, couples must avoid pregnancy for at least three months after the drug is stopped (for men), or after one full ovulation cycle (for women). If a woman gets pregnant while on methotrexate, termination of the pregnancy is advised, if this is consistent with her beliefs. Women should not nurse while taking methotrexate.

BIOLOGIC THERAPY

Biologic therapy has come to the forefront for treating a multitude of disorders. These agents are made from living organisms and their products, such as proteins, genes, and antibodies. Using biologic therapies enables researchers to translate their knowledge of the mechanisms of disease into specific therapies. In August 1998, the FDA approved a biologic therapy for Crohn's disease. Infliximab (Remicade[®]) is approved for moderately to severely active Crohn's in patients who have had an inadequate response to conventional therapy, and for reducing the number of draining enterocutaneous fistulas.

Infliximab is a chimeric (75 percent human, 25 percent mouse protein) monoclonal antibody. This antibody blocks the production of tumor necrosis factor-alpha (TNF-alpha), a cytokine (chemical) that is released by cells in the immune system. Studies have shown that TNF-alpha plays a role in inflammation. In people with active Crohn's disease, there is increased production of TNF-alpha in the intestinal lining, and increased excretion of this cytokine in their stools. Infliximab is the only drug that the FDA

has approved specifically for Crohn's disease. It has been given as a single two-hour intravenous infusion to more than 25,000 Crohn's patients with moderate to severe disease or fistulous disease that resisted other therapies. In the original studies, two-thirds of patients with moderate to severe disease improved, and one-third achieved remission. The second of these studies involved nearly 100 patients with fistulas; some had multiple fistulas. In two-thirds of these patients, most of the fistulas closed; in more than half, all of the fistulas closed. The patients in this study had received three infusions of either infliximab or a placebo over a six-week period. Both studies suggested that a single infusion of the drug was effective in the short-term treatment of moderate to severe, previously resistant Crohn's disease, and that three infusions given in a six-week period were effective in closing most fistulas. Preliminary data suggest that the beneficial effect of infliximab persists when another infusion of the medication is given every two months. A large prospective analysis of reinfusion is being done. (In a prospective trial, the method for analyzing the data has been specified in the protocol before the study begins.)

The effectiveness and possible side effects of infliximab after long-term use are not yet clear. The possibility of allergic reactions to repeated infusions, and even the appearance of malignancies, is being evaluated. Treatment should be reserved for patients who do not respond to conventional therapies.

Mounting evidence, based on clinical experience and preliminary results from research studies, possibly provide support for expanding the indications of infliximab beyond the initial FDA-approved guidelines. Infliximab treatment may be an

effective strategy for tapering patients off steroids; it may be a useful option for maintaining remission. These and other indications for infliximab are being explored as possible treatment alternatives, and physicians await controlled clinical studies to provide solid evidence for the medication's use in these situations.

As of this writing, researchers are assessing other treatments involving cytokines. Some of these therapies involve injections of cytokines that suppress inflammation. Others are antibodies, which block cytokines that promote inflammation, such as anti-TNF-alpha. Preparations under study include interleukin-10 and interleukin-11 in people with active Crohn's disease. Similarly, trials will begin with antibodies that are targeted against interleukin-12 in patients who need steroids and are not responding to other forms of treatment.

MISCELLANEOUS THERAPIES UNDER INVESTIGATION

There has been significant progress in the arena of organ transplantation, with the development of new medications that prevent rejection of transplanted organs. Two of these agents, tacrolimus (FK506) and mycophenolate mofetil, are now being tested in people with IBD. Tacrolimus has been used successfully to treat patients suffering from acute attacks of IBD who had not responded to steroids. In a preliminary report, seven of 11 patients achieved remission rapidly. Similarly, mycophenolate mofetil, combined with corticosteroids, has been shown to be effective for chronic, active Crohn's that has not responded to other therapies.

In small uncontrolled and controlled trials,

heparin, a blood thinner, has demonstrated effectiveness in ulcerative colitis patients who do not respond to corticosteroids. Researchers are not certain why heparin may be effective in IBD. It is possible that the compound interferes with cytokines that cause inflammation.

Omega-3 fatty acids, such those found in fish oils, may have an anti-inflammatory effect. These acids may alter the levels of leukotrienes, compounds that play a role in inflammation. Early studies have shown that omega-3 fatty acids benefit people with active ulcerative colitis, although they do not appear to be helpful in maintaining remission. (One controlled trial has demonstrated that omega-3 fatty acids effectively maintain remission in Crohn's.) This preparation is not available in the U.S. More research needs to be done before we can determine whether this treatment is safe and effective for people with IBD.

Considerable interest has been generated in “probiotic” therapies in people who suffer from pouchitis after undergoing an ileal pouch-anal anastomosis. In this operation, which is performed in people with severe ulcerative colitis, the colon is removed and the surgeon uses part of the small intestine to create an internal pouch, which is joined to the rectum. This allows the patient to continue to defecate normally. This pouch sometimes becomes inflamed—hence the term “pouchitis.” The benefit of probiotics in other forms of IBD has not been demonstrated.

Smoking appears to be protective in ulcerative colitis and harmful in Crohn's disease. In light of these findings, the use of nicotine gum and patches has been attempted in colitis. Nicotine, in high doses, has been shown to be effective in treating active colitis in patients who are previous

smokers; however, its effectiveness for maintaining remission is not well established. The side effects of tobacco and the addictive properties of nicotine use being well known, these treatments remain controversial.

SUMMARY

In general, aminosalicylate pills, enemas, and suppositories remain the first line of therapy for controlling symptoms in people with active ulcerative colitis or Crohn's disease, as well as for maintaining remission. Oral aminosalicylates also may prevent Crohn's from recurring after surgery. Oral corticosteroids are usually reserved for those individuals who fail to respond to aminosalicylates or who require rapid control of symptoms. For patients who are not responding to standard approaches or who require continuous corticosteroids, 6-MP or azathioprine should be considered. These agents are effective for achieving and maintaining remission in both Crohn's and ulcerative colitis. If these cannot be used successfully, methotrexate should be considered, especially in Crohn's. In cases of active, severe ulcerative colitis that does not respond to intravenous corticosteroids, intravenous cyclosporine A may be considered, with the addition of 6-MP or azathioprine, which may reduce the risk for colectomy. Antibiotics may be beneficial in certain clinical situations. Infliximab is appropriate for Crohn's patients who fail to respond to first-line conventional medical therapy or who have fistulas.

There is no standard regimen for managing all people with IBD. The symptoms, course of disease, and prognosis vary considerably. Proper disease management depends upon an accurate diagnosis. This typically requires endoscopic (the use of lighted tubes to view the intestine),

radiologic (x-rays), and pathologic (analysis of tissues) observations. A successful treatment strategy employs not only medical therapy, but careful attention to detail, and judicious use of common sense. Finally, despite advances in medical therapies, some people with IBD eventually will require surgery, either to control their disease or to treat certain complications. Although beyond the scope of this review, surgical intervention is integral to the care of people with IBD, and surgical consultants experienced in IBD are vital to proper management. Knowing when surgery is indicated and how to operate on these diseases is of paramount importance to both the immediate and long-term outcomes. At present, colectomy is the only cure for ulcerative colitis. Unfortunately, Crohn's disease often recurs after resection, but recent studies show that postoperative relapses can be reduced by continuous preventive treatment with aminosalicylates, 6-MP, or metronidazole. For detailed information about the role of surgery in IBD, please ask CCFA for the brochure on this subject.

As active partners in the management of your illness, you and your doctor should discuss, in detail, all of the medical and surgical options available to you. Reading brochures like these and accessing CCFA's Web site (www.ccfa.org) will help you stay informed about the latest therapies and surgical techniques, and give you tips about coping with your illness from day to day. Remember: Hundreds of thousands of people with IBD are living productive, fulfilling lives. With proper care, you can, too.

MANAGEMENT OF THE PEDIATRIC PATIENT

In large part, treatment regimens for children with IBD are based on adult experience. Children require individualized treatment that takes numerous factors into account: the specific disease manifestations (location of inflammation in the intestines, duration, prior response to therapy), the psychosocial adaptation of the child and family, and the child's age and size. Drug dosages also must be tailored, based upon each child's weight.

Children and adolescents are moving through a period of physical and emotional growth and development. Special consideration must be given to potential side effects and to issues of compliance with the prescribed treatment regimen. Regrettably, few well-designed clinical trials have generated data that specifically address the effectiveness of "standard medications" in children. However, the safety profile of these drugs has been supported by many years of use in pediatric clinical practice. Recently, the FDA mandated that the safety and effectiveness of new drugs be established in children and adolescents. Therefore, we anticipate that the number of studies of medications in the pediatric population will be dramatically increasing. All of the medications used for adults with IBD are also used for children, and the indications and contraindications are similar. This section attempts to address the special considerations when the agents described in this brochure are prescribed for children and teenagers.

AMINOSALICYLATES

For treating mild-to-moderate, active ulcerative colitis and Crohn's colitis in

children, 5-aminosalicylate (5-ASA) compounds remain the initial therapy in most cases. Although sulfasalazine clearly is effective, its use has generally declined in favor of mesalamine and olsalazine products, which have fewer side effects. Side effects from sulfasalazine may include headache, sun sensitivity rash, or other signs of sulfa allergy.

5-ASA may be taken rectally or orally. The dosages for a child are extrapolated on a per-kilogram basis from data in adults. The number of pills required (as many as 10-16 per day), and the frequency of administration for effectiveness (3-4 times per day) makes compliance with Asacol[®], Colazal[™] or Pentasa[®] difficult for young patients. The dosage schedule will have to be carefully considered in light of the child's schedule: Should a dose be included or excluded during the school day? Parents may want to involve the child in this decision to aid compliance. Special consideration has to be given to the younger child who is unable to swallow tablets or capsules. A commercially available form of liquid sulfasalazine is no longer available; however, many pharmacies will formulate a suspension if requested. (It is helpful to determine in advance if the local pharmacy can comply with this request.) Additionally, Pentasa capsules may be opened and the contents administered promptly in yogurt or peanut butter.

For the child or adolescent with left-sided colonic inflammation, topical therapy with a 5-ASA suppository or enema often helps, and has minimal potential side effects.

Enema therapy may be a daunting prospect at first, but with education, support, and guidance, many patients and families adapt readily to this treatment.

CORTICOSTEROIDS

Topical Treatment

In the child with mild-to-moderate, active ulcerative colitis with symptoms predominantly of left-sided colitis (tenesmus, a persistent urge to empty the bowel; urgency), rectal preparations of corticosteroids (foam, enema) are often prescribed, along with oral 5-ASA compounds. When tenesmus and urgency are particularly severe, foam is perhaps better tolerated than cortisone enema preparations.

Oral and Parenteral Treatment

When mild-to-moderate, active ulcerative colitis or Crohn's disease do not improve, oral corticosteroids are prescribed on an outpatient basis. Dosages are determined on a per-kilogram basis. Often, sulfasalazine or mesalamine will be continued, in addition to steroids. Once again, the indications and dosages of corticosteroids for children who are more significantly ill and admitted to the hospital are similar to those in adults: Intravenous corticosteroids are administered at the hospital. Once remission is induced, the corticosteroid dosage is gradually tapered, with the goal of discontinuing this therapy. Less commonly, with "steroid-dependent" disease (symptoms that respond only to steroid therapy), small dosages are given daily or every other day.

Side Effects

The cosmetic side effects of corticosteroids may be disturbing to the child and overwhelming to the adolescent, and may lead to poor compliance. Unwelcome side effects may include facial swelling, excessive weight gain, hair growth, and acne. Fortunately, these are temporary conditions that disappear when the dose is lowered or the medication discontinued. Less commonly, with high-dose steroid

therapy, “stretch marks” may result. The puffiness that accompanies steroid therapy can be reduced to some degree by lowering the child’s salt intake.

As in adults, the list of potential side effects of long-term steroid usage in children is extensive. Some of the complications, such as mood swings or personality change and high blood pressure, are most likely related to the higher dosages prescribed. (These complications probably are more common in, although not exclusive to, adults.) In children, linear growth suppression (growth failure) and a decreased supply of the necessary minerals used to build strong bones (bone mineralization) are difficult problems that occur with chronic (long-term) steroid therapy. If the disease is severe enough to require long-term steroid therapy, alternate-day therapy (taking steroids every other day) appears to lessen the impact on linear growth.

To minimize the risk of osteoporosis, it is important to ensure adequate calcium intake in all IBD patients. For patients on chronic steroid therapy or those with chronically active IBD, physicians may recommend a DEXA scan (a special X-ray) to evaluate bone mineral density. Osteonecrosis (bone deterioration) of the hip, although a recognized complication of steroid therapy in adults, is seldom a problem in children or adolescents.

One possible complication of steroid (or other immunosuppressive) therapy is seldom mentioned. This is the risk of overwhelming Varicella (chicken pox) infection. If a “Varicella-naïve” child (one who has not had chicken pox and has not been vaccinated) is taking steroids or 6-MP and is exposed to chicken pox, the child’s physician should be notified immediately. In this case, an injection of

varicella zoster immune globulin (VZIG) would be recommended to limit the potential severity of chicken pox. A full discussion of your child's immunization history with your doctor may help to minimize the risk of this complication.

Steroids do not make children with IBD more likely to suffer from colds or other infections. Similarly, children who have been on steroids do not appear to be at higher risk for adrenal insufficiency if they develop routine viral or bacterial illnesses soon after steroid treatment is discontinued. (Adrenal insufficiency refers to the impaired production of various hormones that the body needs to function properly.)

However, stress doses of steroids should be considered before general anesthesia for surgery and during the ensuing 24 to 48 hours, to protect against potential adrenal insufficiency during the "stress" of surgery.

IMMUNOMODULATORS

The indications, contraindications, and adverse side effects of the immunomodulators, such as 6-MP and azathioprine, are not significantly different in children, when compared to adults. Azathioprine and 6-MP have been widely prescribed as maintenance therapy for Crohn's disease and ulcerative colitis that do not respond to standard medications. It has been shown that 6-MP is effective in children for controlling active disease, for steroid-dependent disease, and for perianal disease. In addition, a newer study suggests that 6-MP may, potentially, be effective in preventing the relapse of Crohn's disease after surgery. The risks and benefits of antimetabolite therapy with 6-MP or azathioprine should be discussed at length with the prescribing physician. However, these drugs should not necessarily be withheld from children based

upon age alone. The steroid-sparing effects of this therapy, as well as its ability to control inflammation, may benefit children with IBD greatly. These treatments can minimize symptoms and optimize growth.

Limited data is available on the use of methotrexate in children with IBD. Its effectiveness in treating active Crohn's disease, as well as its potential as a maintenance drug for Crohn's, has been suggested in the adult and pediatric experience. Extensive use in children with rheumatoid arthritis would suggest relative safety. The significant potential side effect—scarring in the lungs or liver—appears to be extraordinarily uncommon in children. The principal side effect(s) would include nausea, vomiting, or headache following administration. A benefit of this drug is that only one dose per week is required. However, since the preferred administration is by injection, it is potentially a source of aversion for young patients.

BIOLOGIC THERAPIES

New biologic therapies are emerging to treat Crohn's disease. Infliximab (Remicade[®], an anti-tumor necrosis factor antibody) has been studied in a limited number of pediatric patients. The majority of children and adolescents with refractory Crohn's disease appear to respond to infliximab therapy, whether the drug is used to treat inflammatory or fistulizing disease. The limiting factors appear similar to the adult experience: lack of a maintained response, potential allergic reaction, and the fact that long-term side effects (if any) from this drug have not yet been established.

Antibiotics

Specific antimicrobial agents may be beneficial in treating IBD, particularly distal (left-sided) colitis or perianal disease.

Metronidazole is used in children and adolescents with perianal Crohn's disease. It also is used as an alternative, or in addition, to sulfasalazine or steroids for Crohn's colitis. The dosage prescribed depends on the weight of the child and is conveniently given with meals. Teenagers should be told that alcohol and metronidazole do not mix and may result in severe nausea and vomiting. Long-term therapy may lead to reversible peripheral neuropathy (nerve damage), requiring that the drug be stopped.

Ciprofloxacin has been shown to be effective for treating adults with colitis, and is used as an alternative to metronidazole for perianal Crohn's disease. In the past, ciprofloxacin was not recommended for pre-pubescent children; however, prior concerns have not been validated in clinical use in children with cystic fibrosis or IBD, and the drug's safety profile is quite positive.

Nutrition as Therapy

Obviously, adequate nutrition is vital for all children who are actively undergoing growth and development. Additionally, adequate enteral nutrition may be crucial for the healing of inflammation. Therefore, a high-calorie, well-balanced diet is encouraged as part of the general health maintenance for the young IBD patient, but may be quite difficult to achieve. If there is no clear history of lactose (milk sugar) intolerance, eliminating dairy products from the diet is seldom suggested. These foods often constitute a major source of the child's daily caloric intake, and are important sources of dietary calcium—eliminating them may result in malnutrition. Oral nutritional supplements

may be quite beneficial, but are often poorly tolerated for long periods of time. Children may complain bitterly of the unacceptable tastes or refuse the amount needed to achieve the stated caloric goals. Consultation with a nutritionist and involving the young person in ways of optimizing oral nutritional goals may be helpful.

There has been significant evidence to support the use of an elemental diet as therapy for patients with Crohn's disease. An elemental diet is one in which the protein constituents are broken down into their smallest building blocks. Studies suggest that this type of diet may induce remission in pediatric patients with Crohn's disease, particularly newly diagnosed patients, and patients whose disease affects the small intestine. This form of therapy is very safe. However, the unpleasant taste and the alternative of exclusive elemental tube feedings make this therapy unpopular with young children and adolescents.

Nutritional therapy may be of paramount importance in children who experience growth failure. For the child with significant problems with weight gain and linear growth, increased calories can be provided at night, either by nasogastric tube (placed through the nose down into the stomach), gastrostomy tube (placed through the skin into the stomach), or intravenously (via a central venous catheter). Data suggest that supplemental feeding with either regular or elemental formulas is effective in promoting growth in children and adolescents with Crohn's disease. These are special circumstances, which require excellent communication between the patient, family, and health care personnel, to achieve the most effective method of treatment.

OTHER DRUG ISSUES

Antidiarrheal Agents

Many pediatric gastroenterologists would support the use of loperamide (Imodium[®]), to alleviate the diarrhea of IBD if severe abdominal pain or profuse bleeding are absent. Anticholinergic drugs, codeine sulfate or diphenoxylate hydrochloride with atropine sulfate (Lomotil[®]), are not recommended since they may result in significant side effects.

Acne Medications

Acne is a common concern among adolescents in general, and may be worsened or initiated by steroid therapy in young persons with IBD. Isotretinoin (Accutane[®]), is a commonly prescribed drug for refractory or severe acne. However, the safety of isotretinoin in persons with IBD is not clearly established. There are reports of its use without complication, but there also are anecdotal reports of disease flares associated with its use. Potential drug interactions also may be problematic, notably when 6-MP is used with isotretinoin. Clearly, initial therapy for acne would preferably include topical therapy with cleansing agents or antibiotics, followed by oral antimicrobial agents. Isotretinoin should be used with caution and in consultation with all physicians involved. Ideally, steroid-induced acne will benefit by tapering of the steroid course.

Management of IBD in the pediatric patient continues to improve, thanks to advances in therapy and clinical trials of new agents that are being conducted in children and teenagers. We hope that the information provided here will be helpful when patients and their physician consult to determine the most effective course of treatment for each individual case.



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