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Novel and Future Medical Management of Inflammatory Bowel Disease

Robert W. Summers, MD

Division of Gastroenterology and Hepatology, Department of Internal Medicine, 4545 JCP, University of Iowa, Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, USA

If possible, therapeutic strategies should be based on a sound and thorough mechanistic understanding of the disease etiology; however, the cause of inflammatory bowel disease (IBD) remains unknown. Both genetic and environmental factors are involved, but the understanding of their roles and relative importance in pathogenesis is far from clear. The high incidence in identical twins, particularly in Crohn's disease, is the strongest evidence of a genetic influence. The rapid increase in incidence that occurs when immigrants move from a low- to a high-incidence area is the strongest evidence of an environmental influence. Advances in understanding of genetic or environmental factors have yet to have an impact on therapy; however, over the past decade, significant advances in clarifying the immune processes involved in IBD pathogenesis and how they regulate inflammation are being translated into more effective therapy. Still, treatment remains largely empirical, relying upon anti-inflammatory 5-aminosalicylate compounds (5-ASA), corticosteroids, and immunomodulatory drugs. For many patients, these current time-tested therapies perform very well to keep active disease under good control. On the other hand, inadequacies in both efficacy and safety and potentially serious complications and side effects provide a strong impetus to seek new approaches to disease management. Mesalamine and other 5-ASA drugs may induce allergic reactions and renal injury, and they are frequently ineffective in inducing or maintaining a remission. Although corticosteroids are among the most effective agents to reduce active inflammation, they are not effective maintenance drugs, and they cause dozens of adverse side effects and complications that seriously limit their

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E-mail address: robert-summers@uiowa.edu

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utility. Azathioprine and 6-mercaptopurine are only 60% to 70 % effective, and either may cause significant liver injury, bone marrow depression, or pancreatitis. Methotrexate may induce pulmonary or hepatic fibrosis, and it is less effective than other immunomodulatory agents. Beside the drug complications and side effects, the major failing of standard therapy is the fact that the medications just do not work in many patients. Although they have beneficial effects and frequently keep IBD in remission, the treatments fail to be successful in preventing exacerbations, inducing and maintaining disease remission, and modifying the long-term course of the disease.

In this article, new and potentially important treatments are discussed. These measures include the newer biologic agents, probiotics, helminth ova therapy, leukocytophoresis, and bone- marrow and mesenchymal stem-cell transplantation.

Biologic agents

Biologic agents include a wide variety of circulating substances (antibodies against proinflammatory cytokines, T-cell antibodies, anti-inflammatory cytokines, antagonists of adhesion molecules, growth factors, colony stimulating factors, fusion proteins, antisense oligonucleotides, hormones, immunostimulatory DNA (ISS-DNA, CpG oligodeoxynucleotides) that act through influencing key elements of the immune cascade. Most are blocking antibodies directed against proinflammatory cytokines, others reduce local inflammation by reducing migration of leukocytes across vascular endothelium by blocking key leukocyte adhesion factors, and still others appear to stimulate the innate immune system. As knowledge of how to regulate the immune system increases, additional approaches will be explored.

Infliximab

Infliximab is a chimerc IgG_1 monoclonal antibody to tumor necrosis factor (TNF) that is composed of 75% human and 25% mouse sequences. It was rapidly accepted as the prototype biologic agent in Crohn's disease therapy after a single dose produced a response in about 65% of those treated [1]. Its mechanism is still incompletely understood, but two important modes of action are prevention of TNF signaling and induction of apoptosis of lymphocytes and monocytes. At a dose of 5 or 10 mg/kg, remission occurred in 39% and 45%, respectively, at 30 weeks, compared with 21% on placebo [2]. Even though it may be ineffective or responsible for serious complications, its impact on the management of Crohn's disease has been profound. It can dramatically and rapidly improve symptom improvement, reduce local inflammation, close fistulae, and decrease the need for corticosteroids; however, its efficacy is frequently lost because of immunogenicity, and at 1 year, only 25% of patients were responding to infliximab and off corticosteroids. Its use in ulcerative

colitis was recently approved. After 8 weeks of therapy with 5 mg/kg, approximately 38 % of patients were in clinical remission, and the remission was maintained at approximately 20% at 8, 30, and 54 weeks, with evidence of mucosal healing in about 50% of patients at 30 weeks [3]. The recommended dose for Crohn's disease or fistulizing Crohn's disease is 5 mg/kg with an intravenous induction regimen at 0, 2 and 6 weeks followed by maintenance of 5 mg/kg every 8 weeks thereafter.

Adverse side effects include infusion reactions, serum sickness-like reactions, deterioration of congestive heart failure, and central nervous system (CNS) demyelinating disease. It can be responsible for emergence of serious infections, including bacterial sepsis, disseminated tuberculosis, and invasive fungal and other opportunistic infections. Rare cases of hepatosplenic T-cell lymphomas have been reported in adolescent and young adult patients who have Crohn's disease. All cases have been reported in patients on concomitant therapy with immunosuppressive agents. Thus there is increasing interest in attempting to withdraw immunosuppressive agents at a year in order to reduce the risk of developing some of these serious complications of treatment.

Adalimumab

Adalimumab is a fully "human" IgG_1 antibody against TNFα. It also binds to soluble and membrane-bound TNF, fixes complement, and induces apoptosis of mononuclear leukocytes. It is given subcutaneously to persons who have Crohn's disease, beginning with a dose of 160 mg at week 0, 80 mg at week 2, followed at biweekly intervals with 40 mg by 40 mg every other week beginning at week 4. Initial studies indicate that the agent is well-tolerated and has beneficial effects that are similar to infliximab. Clinical remission occurred in 36% and 24% given 160 mg followed by 80 mg every 2 weeks, or 80 mg followed by 40 mg every 2 weeks, respectively, when compared with 12% of patients given placebo [4,5]. It appears to be both safe and effective in patients who have failed infliximab, and its use is not associated with cross-reactivity in patients who have experienced this in response to infliximab infusions. Because it is a humanized antibody, it is less immunogenic, and the rate of antibody formation is low. The response rate is not increased in patients treated with immunosuppressives compared with those who are only on adalimumab. Although unproven, it may not require concomitant immunosuppressant therapy. Increased susceptibility to infection is likely to occur as with other anti-TNF agents. It has not been adequately tested in ulcerative colitis.

Certolizumab

Certolizumab pegol (CDP571) is a pegylated 95% humanized Fab fragment of an anti-TNFα monoclonal antibody. It too is given subcutaneously at a dosage of 400 mg every 2 weeks. It has a high affinity to TNF, but

because it lacks an Fc fragment, it does not induce apoptosis. Nevertheless, studies in Crohn's disease have demonstrated that it can induce a response and maintain remission [6–9]. At 26 weeks, 48% of treated patients were in remission, compared with 29% treated with placebo. It also is effective in infliximab failures, and it does not induce more adverse effects than placebo-treated patients. It appears to be more effective in maintaining clinical remission when used early in the disease course, but it has not been tested in ulcerative colitis.

The adverse effects of the above agents are very much like those that occur with infliximab. It is of interest that several other anti-TNF antibodies failed to demonstrate adequate benefit in Crohn's disease, including CDP571, onercept, and etanercept. The reasons for failure are not well-understood, but might be dose-related, or more likely, caused subtle differences in the mechanism of action.

Natalizumab

Natalizumab is a humanized IgG_4 monoclonal antibody against $\alpha 4$ integrin, and it inhibits interactions between $\alpha 4$ integrin and adhesion molecules expressed on leukocytes and gut vascular endothelial cells. Thus the agent reduces adhesion, recruitment, and diapedesis of leukocytes into sites of chronic inflammation. Immunogenicity of this agent appears to be low. The first controlled trial in Crohn's disease demonstrated that 300 mg monthly infusions were effective in inducing a clinical remission of about 33% at 8 weeks of treatment, and maintaining it at about 40% at 8, 36, and 60 weeks compared with placebo [10]. Although intermittent use may promote immunogenicity, like many other biologic agents, it is hoped that intermittent treatment interruption may be possible with this agent. Natilzumab therapy of multiple sclerosis was well-accepted until three cases in about 3000 treated patients developed fatal progressive multifocal leukoencephalopathy (PML). This disorder is caused by an opportunistic infection caused by the Jacob-Creutzfeld virus, and it uniformly occurred in patients on both natalizumab and an immunosuppressant. The agent was removed from the market, but then reinstated to be used without a concomitant immunosuppressant, and with a stringent registry designed to detect subtle neurological symptoms that might suggest early PML. Whether or not the agent will be approved for Crohn's disease is unknown, but it will depend on the outcome of several ongoing clinical trials and the results of the strict surveillance that is proceeding in multiple sclerosis.

Visilizumab

Visilizumab is a humanized monoclonal antibody that binds to the CD3 antigen on activated T cells; it is a component of the T-cell receptor complex

that does not fix complement. The proposed mechanisms of action from in vitro studies include apoptosis of activated T-cells and downmodulation of cytokine release from resting T cells. It is given as an injection for 2 days, and has been reported to be efficacious in both moderate to severe ulcerative colitis and Crohn's disease [11,12]. At higher doses of greater than 15 mcg/kg, it can cause an acute "cytokine release syndrome" that is short-lived and can be partially ameliorated by giving aspirin. Acceptance will depend on confirmatory evidence from controlled clinical trials.

Probiotics

Trillions of bacteria divided into hundreds of different species inhabit the gastrointestinal tract. Many of these organisms are not even identified or categorized. They are in intimate relationship with the enteral immunologic system and play a key role in priming and forming the developing immune system and in maintaining its homeostasis. The vast majority of bacteria are commensal and do not induce an immune inflammatory reaction; however, they still have the capacity to modulate the immune response and induce intestinal epithelial cells to suppress chemotaxis, downregulate proinflammatory cytokine expression, and increase IL-10 production [13]. The host–bacterial interaction is almost certain to play a role in the pathogenesis of IBD, a role that is called dysbiosis. Antibiotics may affect this relationship in a beneficial way, but a more precise method to influence the ratio of "good" versus "bad" bacteria is to administer large doses of specific microorganisms via the digestive tract.

The beneficial role of probiotics is best exemplified in the case of pouchitis. After colectomy and ileal pouch-anal anastomosis, symptomatic inflammation occurs in the pouch in about 50% of cases. Although antibiotics are usually effective, about 10% of cases are either refractory or frequently recurrent. A preparation containing four species of lactobacilli has been shown to be effective in achieving symptomatic and endoscopic remission in about 85% of cases treated with VSL#3 [14,15]. More investigation is ongoing with other agents and doses, and improvement in results may to occur.

Helminth ova therapy

As noted above, the development of abnormally amplified intestinal inflammation appears to be caused in part by hyperreactive and misdirected immune responses to enteric bacteria. The idea for a new approach to IBD therapy arose from theoretical, epidemiological, and experimental roots. IBD occurs in families of patients with a higher than expected frequency and there is a higher relative risk in identical twins, especially for Crohn's disease [16]. A mutation in the caspase activation and recruitment domain 15 (CARD15)/ nuclear oligomerization domain 2 (NOD2)

intracellular protein product increases the susceptibility of developing Crohn's disease [17]; however, no single gene is responsible for either ulcerative colitis or Crohn's disease, although other genes are being explored. CARD15 accounts for only a few persons who have the disease; most patients who have Crohn's disease do not have the defect, and most persons who have a mutated form do not develop Crohn's disease. As yet, no treatment discoveries have emerged from finding genetic mutations.

Genetic traits affect the risk of developing IBD, but only environmental factors can explain the increasing worldwide incidence of these diseases. Both geography and living conditions have been shown to influence the development of IBD. For many years, an increased North-South incidence gradient, and an increased higher-to-lower socioeconomic status gradient have been recognized as IBD risk factors, but the reason for this observation remains unexplained. IBD is common in industrialized and highly hygienic areas of the world, but uncommon in areas where living quarters are crowded and unsanitary. Helminths have been largely eliminated in most of the Western industrialized world, but continue to colonize people in many parts of the world, including much of Central and South America, Asia, and Africa. It is possible that eradication of helminthic colonization of the gut has increased the risk of developing autoimmune disorders such as IBD by eliminating a protective parasitic influence, and that reintroducing helminths in persons who have active disease would inhibit dysregulated immune-mediated mucosal injury [18].

Helminths have the capacity to prevent excessive inflammatory responses [19]. Parasitic worms inhibit immune responsiveness in naturally colonized humans and various types of experimental colitis in laboratory animals [20]. One proposed mechanism was that helminths altered the Th1-Th2 balance. They have been demonstrated to induce lymphocyte subtypes that produce increased cytokines. Thymus derived lymphocytes that express CD4 surface molecules are known as helper T cells. The Th1 and Th2 subsets are prolific cytokine producers. Helminths induce Th2 type anti-inflammatory cytokines such as interleukin (IL)-4, IL-5, IL-9, and IL-13. These Th2 cytokines are often manifest clinically by increased immunoglobulin E (IgE), increased numbers of mast cells and eosinophils and increased IL-10. Helminths also inhibit production of Th1 cytokines, IL-2, Il-12, TNFa, and interferon g (IFNg). Although these changes occur, this explanation of the inhibitory helminthic mechanisms is incomplete, and does not explain how helminths would improve diseases that are not characterized by Th1 hyperreactivity, such as ulcerative colitis, or allergic disorders, such as asthma. Recent observations demonstrate that helminths also induce regulatory substances and cytokines such as prostaglandin E_2 (PGE_2), IL-10, and tumor growth factor (TGF)-β that exert immune suppression. It appears that regulatory T cells exert a major role in maintaining balance between pro- and anti-inflammatory factors, and achieve immune tolerance largely through the suppression of effector cells and

downmodulating their effector function. Thus helminths possess an important capacity to limit immune reactivity and induce peripheral tolerance by increasing production of regulatory T cells. A transcription factor, FoxP3, in these naturally occurring regulatory T cell plays a role in their development, and also induces secondary suppressor T cells that secrete high levels of IL-10 or TGF-β. These immunomodulatory mechanisms of helminths in rodents have been explored in a series of studies, and are summarized in a recent article [21]. In addition to mechanistic studies, a number of laboratories have demonstrated reduction or prevention of gastrointestinal inflammation when experimental animal models of colitis or gastritis were treated with intestinal helminths [22–26].

A helminth chosen for clinical trials should have the following characteristics

Colonization should be self-limited, and spontaneous elimination should occur in only a few weeks.
There should be no systemic phase, and the helminth should not multiply in the host.
The helminth should not be directly transmissible, and eggs should not be infective until they incubate outside the body for several months.
The helminth should be readily obtainable from animals grown in a controlled, pathogen- free environment.

The organism *Trichuris suis*, known as the porcine whipworm, possesses all of the above criteria that support its safety profile. In a small pilot study, a single dose of 2500 *T suis* eggs was given to a small group of seven patients who had either ulcerative colitis or Crohn's disease. All seven subjects experienced a temporary improvement followed by a relapse; however, longer courses of therapy produced clinical improvement for several months without any detectable adverse effects. These results prompted larger clinical trials [27].

A larger open trial was performed in 29 patients who had active Crohn's disease (Crohn's disease activity index [CDAI] ranged between 220 and 450) by giving them 2500 *T suis* ova by mouth every 3 weeks for a total of 24 weeks [28]. Most patients had long-standing disease and were refractory to standard therapy. Patients ingested 2500 *T suis* ova every 3 weeks, and dosing of all other medications was held constant. Four patients withdrew at or before week 12 because of disease activity, and 1 withdrew between weeks 12 and 24 because of pregnancy. At week 12, 22 patients (76%) responded (as defined by a decrease in CDAI by greater than 100 points or a decrease in CDAI of more than 150), and 18 of /29 (62%) were in remission (as defined by a CDAI of less than 150). At week 24, 23 patients (79%) experienced a response, and 21 of 29 (72%) were in remission. The mean initial CDAI of the responders was 286 ± 51. It decreased to 96 ± 51 at week 12 and 99 ± 37 at week 24. Thus the mean improvement in CDAI for these patients was 190 and 188 at weeks 12 and 24, respectively. There were no side effects or complications attributable to therapy, and of multiple

laboratory values monitored, only the eosinophil count increased from 152 $\pm$ 23 to 212 $\pm$ 54 ($P < .05$). Disease location, disease duration, use of other IBD therapies, and tobacco use did not affect outcome. No adverse clinical effects occurred as a result of therapy, and no patients had to be treated with an anthelmintic for worsening disease activity or suspicion of adverse side effects attributable to the parasite.

A double-blind controlled clinical trial was performed in 54 subjects who had active ulcerative colitis [29]. Subjects were treated with an orally administered a dose of 2500 eggs in a sport drink with charcoal, or the placebo vehicle every 2 weeks for 12 weeks. *T suis* ova induced major improvement in these patients in comparison with those treated with placebo. Using intention-to-treat, a favorable response (defined as a fall in the ulcerative colitis disease activity index $\geq$4) occurred in 13/30 (43%) of the subjects treated with ova and 4/24 (17%) of the placebo-treated subjects, $P = .04$. The initial ulcerative colitis disease activity index (UCDAI) of the 13 patients who responded to ova decreased from 8.8 $\pm$ 0.4 to 2.8 $\pm$ 0.4 at 12 weeks. The differences in remission rates between the two groups did not achieve statistical significance. Of the 13 ova-treated patients who responded, 6 attained a UCDAI of 2 or less, compared with two of the four placebo-responders. Subset analysis was limited because of the small sample size; however, there was a trend that patients who had total colonic involvement and shorter durations of disease activity were more likely to respond to ova therapy. The data from another clinical index (Simple Index) that could be measured at every clinic visit indicated that the therapeutic response to the agent occurred in about 6 weeks. The study was continued for an additional 12 weeks (Phase II) by treating each group of patients with the alternate therapy while maintaining the double blind. In this crossover phase, fewer patients (49) entered, because 5 chose not to continue, and only patients who had active disease at the beginning of Phase II were analyzed. At the end of Phase II, 56% given *T suis* ova responded, whereas only 13% improved with placebo ($P = .02$). Combining data from both 12 week periods (Phases I and II) showed a 47% response with ova and 15% with placebo. It was of interest that of the 13 subjects who responded to the active treatment in Phase I, 6 remained in remission for the 12 week of placebo therapy, 6 suffered relapse, and 1 dropped out. There were no side effects, complications, or changes in laboratory values attributable to the therapeutic agent in either the first or second 12-week periods.

Conclusions from clinical trials with *Trichurus suis ova*

The studies described above included over 100 patients who had initially active disease, and demonstrated that *T suis* ova therapy is safe and effective in both ulcerative colitis and Crohn's disease. Many had disease that was long-standing and refractory to conventional medications, and benefit occurred whether the treatment was given alone or in conjunction with other

IBD drugs. Many patients were treated effectively well beyond the study periods, some for more than 3 years. Thus the agent appears to be effective not only in treating active disease, but also in maintaining remission. Withdrawal of the treatment resulted in relapse over variable time periods, and thus the therapy appears to have a suppressive effect on the immune system. Finally, no adverse clinical effects occurred that could be ascribed to therapy, and thus safety and tolerability appear to be high. Another helminth, hookworm or *Necator americanus*, is also being investigated in a controlled trial of active Crohn's disease in Nottingham, England [30]. Because the use of helminths is an entirely new approach to therapy, many issues remain for use of helminths in IBD. Some of these are listed in Box 1.

Alternative and complementary medications

Although physicians do not prescribe the majority of alternative and complementary therapies in IBD, it is becoming increasingly recognized that their use by patients over the past 20 years has increased significantly, in up to 68% of patients in the United States and Canada. Unfortunately, the usefulness of these treatments is almost impossible to ascertain because of the paucity of adequate controlled clinical trials. Thus, both physicians and their patients are forced to rely on anecdotal reports of benefit or harm. Most patients do not regard the lack of scientific evidence as a problem, and many would likely continue using these approaches even if clinical trials showed that they were ineffective. Unfortunately, some of the treatments not only are of no benefit, but they may cause significant problems, including aggravation of symptoms and interference with the effects of other medications, and their lack of approval by regulatory agencies allows the inclusion of harmful impurities. The supplements listed in Box 2 are the most likely to be of benefit and the least likely to be harmful. Herbal therapies may be the most hazardous, and the naturopathic therapies may be the

Box 1. Considerations on use of helminths in inflammatory bowel disease

Confirmation of results in larger trials
Active versus maintenance therapy
Dose response and timing of doses
Use in high-risk subjects as prophylaxis
Efficacy of other helminths
Effects of secretory extracts/fractions
Short- and long-term safety
Use in other immune-mediated diseases
Adjunctive/complementary therapy
Investigation of mechanisms of action

Box 2. Alternative approaches to treatment of inflammatory bowel disease

Supplements
Protein
Zinc
Selenium
Vitamins A, E, B complex
Vitamin B12 and folic acid
Lycopene
Glutamine
N-acetyl glucosamine
Omega 3 fatty acids
Flavinoids

Herbs
Cat's claw
Gingko
Goldenseal
Marijuana
Slippery elm
Tumeric (curcumin)
Wild indigo
Green tea
Aloe-derived mucopolysaccharide
St. John's wort
Boswellia serrata
Echinacea
Tylophora

Naturopathies
Hypnotherapy
Chiropractic
Aroma therapy
Acupuncture, acupressure
Reflexology
Homeopathy
Bioelectromagnetism
Relaxation therapy
Massage relaxation therapy
Hydrotherapy
Clinical nutrition
Physiotherapy
Touch therapy

most like placebo. It is imperative that health care workers ask their patients if they are using unproven or unapproved treatments and be aware of the potential problems that they may cause. Unfortunately, there is little scientific information to judge the effect of these approaches to treatment; however, physicians should keep an open mind about their potential. Without data, it is not possible to evaluate their effect or recommend their use.

Leukocyte filtration

The discussion to this point has focused on administering various therapies by mouth, injection, or infusion. Investigation has also explored modifying the immune environment by other means, including leukocytophoresis, extracorporeal photoapheresis, and bone-marrow and stem-cell transplantation. Most of the work has been done on selective leukocyte apheresis [31–33]. The two most common techniques employed passing peripheral blood through an external column or filters and returning it through another line. The Adacolumn (JIMRO, Gunma, Japan) is made of cellulose diacetate beads and removes 65% of granulocytes, 55% of monocytes, and 2% of lymphocytes. Cellsorba (Ashahi Kasai Medical, Tokyo, Japan) is composed of two nonwoven polyester fiber filters, and it traps 100% of granulocytes, 60% of lymphocytes, and 35% of platelets. Centrifugal cell separators have also been used, but the number of cases and the methods used make interpretation of the data difficult. Granulocytes, monocytes, and lymphocytes play an important role in initiating and maintaining the inflammatory reaction. Removing these cells favorably modifies the cellular immune response. The process does more than decreasing the number of cells. The programmed leukocytes removed are replaced by naïve immunocytes from the marrow or peripheral blood. The process also decreases expression of adhesion molecules and reactive oxygen species, reduces cytokine production, and alters the function of white blood cells and dendritic cells.

Unfortunately, few controlled clinical trials have been done, patient groups have been heterogeneous, and many of the published studies are methodologically flawed, so that it is difficult to evaluate the results of therapy. Therapy is usually given weekly or biweekly. Results with the Adacolumn in ulcerative colitis range from responses of 60% to 80%, and remission rates of 20% to 90 % after 3 to 20 weeks of therapy are reported. With the Cellsorba system, the improvement or response rates range from 60% to 80%, and remission from a single study was reported as 65%. Studies are very limited in Crohn's disease, but suffer from similar methodological deficiencies. With the Adacolumn, responses or improvement occurred in 50% to 100%, and remission occurred in 15% to 60%. With Cellsorba, about 75% improved and 50% entered remission. The duration of response in either ulcerative colitis or Crohn's disease is essentially impossible to determine because of the uncontrolled nature of the studies—it ranges from 2 months to nearly 2 years. One constant feature of all of the reports is

the almost total absence of adverse effects. Such a study is in progress in the United States and the most recent review of these methods is useful [31].

Bone-marrow and stem-cell transplantation

There is a limited body of information regarding bone-marrow and stem-cell transplantation. A report of six patients who had Crohn's disease and leukemia and who were treated with allogeneic marrow transplantation was published in 1998. Four of five patients followed for 6 to 15 years remained free of Crohn's disease (one patient died of sepsis and one had a relapse of Crohn's disease after 1.5 years). Two patients who had long-standing ulcerative colitis, psoriasis, and leukemia underwent allogeneic stem cell transplantation, and all three of these disorders were in remission for 4 years after transplantation. Not all patients reported have experienced remission of their IBD, and some have experienced deterioration of their condition or death; thus the outcome of long-term benefit is not established, and a number of issues remain before this becomes an acceptable form of therapy.

Summary

The clinical appearance of biologic agents represents a milestone in the understanding of the inflammatory process. They permit modification of the basic elements of the immune process. There is a vigorous debate over when in the clinical course of the disease the biologic agents should be administered. Both the traditional "step-up" versus the more recent "top-down" approach have proponents and opponents. The top-down approach has taken its lead from the discipline of rheumatology, where it is argued how important it is to prevent irreversible anatomic joint changes in the joints by giving biologic agents early in the course of the disease. Arguments for the step-up approach include the frequent loss of prolonged beneficial effect, the development of systemic and local immune reactions to administration, the risk of developing serious infections, and the extremely high cost of administration. These provide strong arguments that the agents should be given when other more standard agents are no longer effective. The occurrence of lymphomas may be increased in patients on concomitant immunosuppressive therapy, and if it can be avoided, that complication may occur less frequently. The controversy about timing is not settled, and it is likely that multiple strategies will be tested to find the most cost-effective approach.

Probiotics are attractive because they represent a "natural," safe, and relatively inexpensive approach; however, it is difficult to be enthusiastic about their potential when the majority of controlled studies have failed to demonstrate any therapeutic benefit in IBD. It remains possible that the results may have been influenced by the bacterial species used. Some species or combination of species might have a greater immunomodulatory

effect, and the quantity of the bacteria administered might have a profound effect on the clinical outcome. The stage and location of the disease may also affect the response to treatment. Because the use of probiotics in the treatment of active Crohn's disease or ulcerative colitis has not been successful, further investigation is necessary before this mode of therapy is employed in any disorder except pouchitis.

Helminth ova therapy is also an attractive therapy because of its apparent safety, "natural" mechanism, and ease of administration. Preliminary experience has been encouraging, but larger studies are required to confirm not only efficacy, but also safety. It is not approved by the Food and Drug Administration, and must be considered an experimental therapy. Many details of its use remain to be elucidated, but further investigations are being planned. Helminth therapy could be complementary to drug therapies, and may be used in combination with other more traditional therapeutic agents commonly used to manage IBD. It is possible that *T suis* ova therapy might be especially beneficial as maintenance therapy, because it is likely that it may be easier to maintain a noninflamed bowel than to reign in a highly active one.

Alternative and complementary therapies are increasingly being used by patients, and usually without their physicians' knowledge or recommendations. Because of the lack of factual information about the efficacy and safety of these approaches, it is very important for clinical trials to be done so that physicians and their patients can make informed decisions about their use.

The removal of the immunocytes from the circulation is relatively new, and much remains to be investigated before leukophoresis becomes a standard of treatment. Although the results of many reports are encouraging, the potential of this therapy cannot be evaluated until adequate multicenter, placebo-controlled clinical trials are done according to current standards acceptable to judge clinical outcomes in comparison with standard drug trials.

Bone-marrow and stem-cell transplantation is an extreme procedure with many inherent hazards. Issues such as separating the effect of intense immunosuppression from the effect of the transplantation, the type of transplantation (bone marrow or peripheral stem cell), the choice of conditioning regimens, the type of patients selected, the degree of informed consent, and patient protection all must be considered before this approach is considered for more widespread use; however, it is possible that this approach may be applicable under certain conditions.

It is anticipated that safer and more effective treatments will emerge as our understanding of the interactions between genetics, the environment, and regulation and dysregulation of the immune process increases. There are reasons to be optimistic, because new agents will be chosen according to strict criteria to satisfy the regulatory agencies; from these explorations, continued therapeutic advances will be made that will result in improved quality of life, reduced permanent anatomic damage, and fewer surgical procedures. With advances, however, problems may also arise, because

the newer agents are more effective in modifying basic immunological processes. By reducing inflammation, we may interfere with immune surveillance of malignant processes, render the patient even more vulnerable to serious infections, and unveil unanticipated problems that the immune system is meant to keep in check.

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