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Therapeutic Targets for Emerging Biologic Therapies in IBD

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Activity Overview

Biologic therapies, which target different aspects of the inflammatory cascade than existing therapies, are changing the treatment of inflammatory bowel disease (IBD). In addition to inducing and maintaining remission, biologic agents have demonstrated steroid-sparing and mucosal healing properties, as well as the ability to improve patient quality of life. Moreover, these agents have been associated with reductions in hospitalizations and surgeries for Crohn's disease. Despite these benefits, clinical use of the available biologic agents is limited because a proportion of patients do not respond to therapy, experience a rapid loss of response, or risk developing serious toxicities. This activity reviews the mechanisms of action and presents the latest information on the safety and efficacy of the available biologics. Currently, several new biologic agents are in various stages of investigation for use in IBD patients. To appreciate the potential advances offered by these biologic therapies, clinicians should understand the therapeutic concepts behind these agents and how they differ from existing treatments. This CME supplement has been designed to increase awareness and understanding of the current and evolving therapeutic armamentarium available to effectively treat patients with IBD.

Target Audience

This activity has been designed to meet the current educational needs of gastroenterologists and other clinicians who manage patients with IBD.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Describe the mechanisms of action of existing and novel biologic agents used in the treatment of IBD
- Compare and contrast how different biologic agents target unique aspects of the inflammatory cascade
- Evaluate the clinical efficacy and safety of current biologic therapeutic options for the management of IBD
- Summarize the therapeutic need for the novel biologic therapeutic options under development, as well as their potential efficacy and risks

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Medium

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Therapeutic Targets for Emerging Biologic Therapies in IBD

On February 2, 2009, a group of nationally prominent clinicians and researchers convened to discuss relevant issues regarding the mechanisms of action and roles of current and investigational biologic therapies for patients with inflammatory bowel disease (IBD). The pathogenesis and natural history of IBD were presented as a framework for understanding the therapeutic actions and potential targets of current and future biologic agents. Current biologic agents were addressed, with specific focus on how these agents may alter the natural history of disease and their role in current and evolving treatment paradigms. Other topics included the risk-benefit profile of current biologic agents, the therapeutic need for novel biologic agents, and the positioning of these novel agents. This supplement, which summarizes the discussions from the meeting, is intended to provide insight into the role of current biologic agents and promote understanding of how emerging novel biologic agents may shape future treatment paradigms for patients suffering from this chronic, debilitating disorder.

Mechanism of Action of Biologic Therapies: Targeting the Inflammatory Cascade

The development of IBD is widely accepted as being a consequence of a dysregulated mucosal immune response to the enteric microbiota and corresponding microbial antigens in the gut of a genetically susceptible individual.[1-4] Although researchers have long recognized this complex interaction among genetics, the immune system, and the environment, the understanding of the contribution of each of these factors to IBD pathogenesis continues to evolve. In addition to providing insight into the heterogeneous clinical presentations of IBD, the diversity of these interactions may help explain the lack of a universal response to any single therapeutic agent.[5]

Pathogenesis of IBD

Recent experimental and clinical evidence has confirmed that abnormal host–microbial interactions in the intestinal mucosa play a pivotal role in the initiation and pathogenesis of IBD.[3,6] "There is a fundamental problem," explained Dr. Scott Plevy, "in how the immune system reacts to the enteric microbiota, which is an incredibly large mass of microorganisms that normally colonize all of our guts." Though our understanding of the diversity and complexity of the microbial flora remains incomplete,[6] many studies indicate that *dysbiosis*, an imbalance between protective and harmful bacteria, is also involved in the development of IBD.[1] Specifically, recent studies have described decreased microbial diversity, increased numbers and virulence of commensal bacterial species (such as *Escherichia coli*), and decreased *Clostridium* species in the intestines of IBD patients.[3,4]

The intestinal epithelium, which is in constant communication with the luminal flora and the underlying cells of the innate and adaptive immune systems,[6] is the first line of defense in the mucosal immune system.[2] A subset of patients with IBD, however, appear to have genetic defects in mucosal barrier function and gut permeability[2] that lead to increased bacterial adherence and inappropriate exposure of the mucosal immune system to bacterial products, which in turn causes inflammation.[1,3,4] This process may be mediated by enhanced activity of Toll-like receptors.[4] Two genes that affect mucosal permeability—the IBD 5 gene organic cation transporter (*OCTN*) and the guanylate kinase *DLG5* gene—have been recognized in the pathogenesis of Crohn's disease (CD).[4] "A simple way of thinking of this," Dr. Plevy explained, "is that you have all of these bacteria that are capable of activating immune pathways if present in any other organ in the body, and they are separated by one epithelial cell (which in fact is immunologically active) from the largest immune organ in the body (the mucosal immune system), so this is an accident waiting to happen."

Although research in IBD pathogenesis has traditionally focused on the role of the adaptive immune system, recent genetic advances highlight a more pivotal role for the cells of the innate immune system, the body's nonspecific defense against pathogens.[1,6] Dr. Plevy explained that "one of the lessons of genetics is that the initiation of events in IBD is likely a result of defects in the more primitive form of immunity—the innate immune system—in first encountering these bacteria." Genome-wide association studies have identified more than 30 distinct susceptibility loci for CD, with polymorphisms in the nucleotide-binding oligomerization domain containing

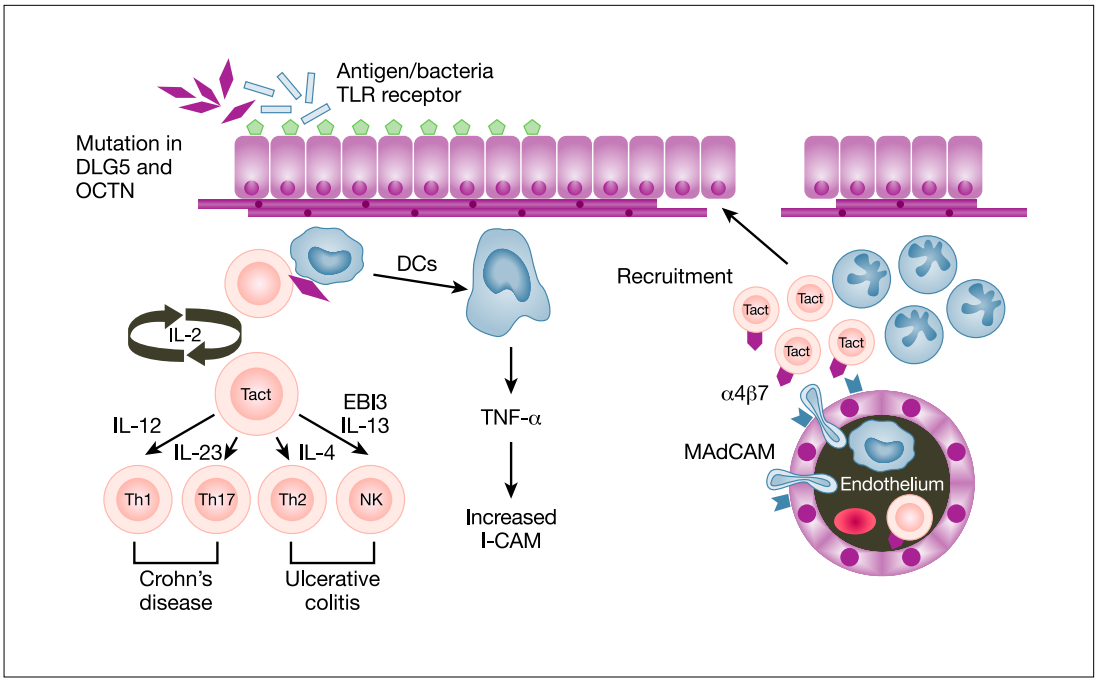

Figure 1. Pathogenesis of IBD.[4]

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2 (*NOD2*) gene being the first described.[5,7] Because the *NOD2* protein is involved in the intracellular recognition of bacterial products, the identification of *NOD2* as a susceptibility gene for CD supports a role for altered intracellular processing of bacterial components in IBD.[5] Recently, two genes involved in autophagy ("self-eating")—a biologic process of membrane trafficking that is important for cellular homeostatic functions—have been linked to Crohn's susceptibility. Recent work has demonstrated that autophagy is an important host defense pathway for killing certain intracellular bacteria, further emphasizing the key role of the innate immune system in the disease process.[5]

Once the innate immune system is activated, bacterial antigens are presented by antigen-presenting cells (such as dendritic cells) to various T-cell and B-cell populations of the adaptive immune system, which perpetuates the tissue damage in IBD patients.[1,5,6] Various inflammatory T-cell subtypes then generate a cascade of immunologic events that lead to chronic mucosal inflammation and IBD, with CD historically thought to have a predominantly Th1 cytokine profile (interferon-gamma production) and ulcerative colitis (UC) linked with a Th2 cytokine profile (interleukins-4, 5, and 13).[1,4,5] Additionally, a third set of T-helper cells, Th17 cells (which produce the proinflammatory cytokines IL-6 and IL-17), was recently identified as an important mediator of the T-cell response in chronic intestinal inflammation.[2,4] A working hypothesis of the pathogenesis of IBD is summarized in Figure 1.

The contribution of environmental factors to IBD remains poorly understood. Dr. Bruce Sands noted that "the most intimately related factors to increase susceptibility to the diseases are factors that affect the gut flora, and most people believe that diet is going to be a critical factor in shaping the microbiota of the gut. However, what factors in the diet shape the microbiota and how they do that is really not well understood." The protective association of smoking with UC has been documented in many studies, with current smokers 40% less likely to develop UC than lifelong nonsmokers.[8] In contrast, smoking appears to be a risk factor for CD.[8] Other epidemiologic data support a protective role for appendectomy and UC development; however, there is a weak association of IBD with factors such as breastfeeding (decreasing risk) and oral contraceptive use (increasing risk of CD).[8] The hygiene hypothesis is an evolving theory that suggests that lack of exposure to helminthic infections during childhood may lead to inappropriate immune responses when an individual is exposed to

helminthic antigens later in life, predisposing individuals to various autoimmune conditions, including IBD.[2,9]

Natural History of IBD

A progressive and destructive disorder, CD eventually results in complications that lead to persistent and refractory symptoms, multiple surgeries, and impaired quality of life.[10,11] However, speaking to the heterogeneity of the disorder, Dr. Sands explained that "for some patients, these diseases do not progress to any significant complication. Patients may have waxing and waning symptoms that may be treated with medications or sometimes just by lifestyle alterations." In fact, longitudinal data from a population-based study of 373 patients with CD in Copenhagen County, Denmark indicate that despite nearly 80% of patients having high disease activity at diagnosis, over half of patients are in clinical remission in any given year.[12] Moreover, data from a cohort of 354 IBD patients in Olmsted County, Minnesota demonstrated that fewer than 50% of patients ever require therapy with corticosteroids.[13]

In contrast, Dr. Sands noted, "the patients we worry very much about are the ones with CD who have progressively more complicated disease behaviors. These patients evolve from an inflammatory phenotype, which certainly does cause symptoms and some temporary disability, to one or more complications, either a stricturing or perforating complication such as an abscess or fistula." Indeed, it is thought that most patients with CD eventually develop a stricturing or penetrating complication. Cosnes et al reported that (among a cohort of over 2,000 patients) only 12% of patients were estimated to be free of either type of complication 20 years after diagnosis.[14] Accordingly, other data support that as many as 70% of patients with CD have surgery within 15 years of diagnosis, with many developing recurrences and eventually requiring more than one operation.[11] More recently, Loly et al found that nearly 60% of patients with CD developed disabling disease within 5 years of diagnosis.[10] In this retrospective cohort of 361 CD patients, severe disease was defined as the need for at least two small-bowel resections (or a single small-bowel resection greater than 50 cm), any colonic resection, construction of a definite stoma, or development of complex perianal disease.[10]

Another key concern for IBD patients is the development of colorectal cancer (CRC), a well-documented complication of long-standing UC. Factors known to increase the risk of CRC in UC patients include long duration of disease,[15,16] family history of CRC,[17] extensive colonic involvement,[18] and primary sclerosing cholangitis.[19] Additionally, severity of colonic inflammation is increasingly recognized as an important risk factor for CRC in UC.[20,21]

Can We Predict the Natural History of IBD?

Currently available tools for identifying patients that will develop aggressive disease are imprecise; however, a number of increasingly accurate clinical prognosticators have been developed. For example, Dr. Sands commented, "the need for corticosteroids, particularly early in the course of disease, is associated with more aggressive disease, worse outcomes over time, and a higher likelihood of disability." In addition to early steroid use, other factors that have been correlated with the risk of early aggressive disease course in CD include age below 40 years, perianal disease at diagnosis, and ileocolonic location.[10,22] Further, weight loss of more than 5 kg and stricturing behavior at diagnosis appear to be independent predictors of poor outcomes (ie, multiple bowel resections, stoma, complex perianal disease), suggesting the presence of nonreversible damage caused by the disease.[10]

Given the low predictive power of these prognostic factors,[10] the addition of biologic markers may be useful in predicting aggressive disease phenotypes. Among patients with CD, the presence of serologic markers—such as anti–*Saccharomyces cervisiae*, anti–*Escherichia coli* outer membrane porin (Omp) C, and anti-I2—has been correlated with severe, complicated disease phenotypes (ie, fibrostenosing or perforating disease or small-bowel surgeries), with the risk of such complications increasing with the number and magnitude of antibody responses.[23,24] Specific polymorphisms of the *NOD2* gene have also been correlated with the presence of fibrostenosing disease of the small bowel in CD patients.[25] High levels of perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been associated with UC-like colonic disease in CD[26] and the development of pouchitis after ileal pouch-anal anastamosis in UC patients.[27]

The impact of treatment on the natural history of IBD remains uncertain. The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry is a prospective, observational registry designed to evaluate the long-term safety of various treatments.[28] Among the 6,290 CD patients enrolled as of August 2004, mortality rates were similar among infliximab-treated and non–infliximab-treated patients. The use of prednisone (odds ratio [OR]=2.13, P=0.007) and narcotic analgesics (OR=1.84, P=0.044), however, was associated with increased mortality. When adjusted for other factors, mortality was independently associated with age (OR=1.07, P<0.001) duration of disease (OR=1.03, P=0.006), and use of prednisone (OR=2.10, P=0.016). Reiterating the consistency of the latter finding, Dr. Sands commented that "the use of steroids has been reproducibly found to

be a predictor for poorer outcomes whether we're talking about disease outcomes or complications such as infection and death in a number of studies."

Review of Mechanism of Action of Biologic Therapies in IBD

Existing Biologic Therapies

Anti–Tumor Necrosis Factor Agents. Although knowledge of the role of tumor necrosis factor (TNF) in IBD pathogenesis has evolved over the decade since the FDA's approval of infliximab, the mechanism of action of the anti-TNF agents remains incompletely understood. TNF is a trimeric cytokine that binds to two TNF receptors (TNF-R1 and TNF-R2), initiating a series of intracellular events that ultimately induces genes responsible for biologic activities such as cell growth and death (ie, apoptosis), development, oncogenesis, immune, inflammatory, and stress responses.[29] Dr. Stephan Targan further explained that the "interaction of TNF with these receptors activates inflammatory cell populations to upregulate more inflammatory molecules such as IL-1, interferon-g, and even some involved in enhancing leakiness of the epithelial cell barrier and breaking down tight junctional function." Both types of TNF receptors can also be released in a soluble form, which can either neutralize or increase TNF activity by binding to circulating TNF. Commenting on the wide range of biologic activities influenced by TNF, Dr. Targan noted that "TNF has enormous protean manifestations in biologic systems as well as in amplifying the immune system."

The beneficial effects of the anti-TNF agents in IBD patients have been attributed to multiple mechanisms, including reverse signaling through membrane-bound TNF and induction of apoptosis in immune cells.[30] Abundant evidence indicates that infliximab induces apoptosis in immune cells,[31,32] and recent *in vivo* observations suggest that absolute levels of apoptosis induced by infliximab correlate with clinical response.[32] However, clinical data demonstrating efficacy of certolizumab pegol, a pegylated Fab' fragment that does not induce apoptosis,[30] suggest that apoptosis cannot be the sole mechanism responsible for the beneficial effects of the anti-TNF agents in IBD. Moreover, the impact of other molecular differences among the anti-TNF agents on IBD patients remains uncertain. Commenting on the failure of the anti-TNF agents etanercept and onercept in CD, Dr. Targan noted that differences could relate "not only to the avidity of TNF receptor binding, but also to differences in reverse signaling, or the on-off rates of these molecules. That is, the faster the on-off rate, the less likely the molecule may reverse signal and stun those cells."

Anti-Adhesion Molecules. The use of anti-adhesion molecules in IBD represents a "noncytokine" approach to therapy designed to limit the recruitment of inflammatory cells to the bowel.[33] Leukocyte recruitment, which plays a central role in the initiation and progression of IBD, is tightly regulated by families of cell-adhesion molecules—including integrins, selectins, and chemokines—that are expressed on the surface of endothelial cells and intracellular spaces.[34,35] Dr. Plevy explained that integrins "recognize receptors expressed on vascular endothelium at sites of inflammation, and specifically the gut, in the case of some specific integrins. When the leukocyte 'ZIP code' recognizes its 'mailbox' on endothelial cells, a signal is delivered that tells the cell that it's time to adhere to the vascular lining and to actually squeeze between the vascular cells and go to the gut, where they create the damage that we ultimately call IBD."

Natalizumab, a recombinant humanized monoclonal antibody against human □4 integrin, is the only selective adhesion molecule inhibitor currently approved for IBD. Natalizumab blocks the interactions of both $\square_4\square_1$ and $\square_4\square_7$ integrins on circulating leukocytes with their receptors, vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1), respectively.[36] Because VCAM-1 is "expressed throughout the body at sites of inflammation," explained Dr. Plevy, natalizumab "not only keeps inflammatory cells from gaining access to the gut but also to sites of inflammation in other parts of the body. This is the reason we think natalizumab is effective in CD as well as in multiple sclerosis." The interaction of $\square_4\square_7$ integrin with MAdCAM-1, however, is specific for endothelium with leukocytes destined to home to the gut, as MAdCAM is not expressed on vascular endothelium anywhere in the body outside of the gut.

Investigational Biologic Therapies

Despite the significant impact of the anti-TNF agents on patients with refractory CD and UC, the variable magnitude and duration of response to these agents continues to prompt the development of new biologic agents for IBD.[1]

Like existing biologic therapies, the biologic agents currently in development are not disease specific, but rather target events downstream of the inflammatory cascade.[2] Given the pivotal role of T cells in promoting the immune response in IBD, many therapies for IBD are aimed at inhibiting T-cell function, blocking T-cell proinflammatory cytokines (eg, interferon □, interleukin [IL]-12/23), or inducing apoptosis of T cells or a subset of these cells.[1] Table 1 summarizes the types of biologic agents under various stages of development; Figure 2

Table 1. Investigational Biologic Agents for IBD[1]

Mechanism	Compound	Target	Compound Class	Development Status
T-cell blockade	cM-T412	CD4 on T-cell surface	Chimeric mAb	Phase 1/2
	Visilizumab	CD3 on T-cell surface	Humanized Fc IgG2 receptor non-binding mAb	Phase 1/2
Blockade of T-cell differentiation or activation	Abatacept	Blockade of CD28 costimulatory pathway	Soluble recombinant fusion protein	Phase 3
	Tocilizumab	IL-6 receptor	Humanized mAb	Phase 1/2
	Fontolizumab	Inteferon g	Humanized mAb	Phase 1/2
	ABT-874/J695	IL-12/IL-23,p40	Humanized mAb	Phase 1/2
	Ustekinumab	IL.12/IL-23,p40	Human mAb	Phase 1/2
	Apilimod mesylate	IL-12/23	Small molecule	Phase 1/2
	Ch5D12	CD40 on antigen-presenting cells	Chimeric mAb	Phase 1/2
Regulatory T-cell modulation	IL-10	IL-10	Recombinant human cytokine	Phase 1/2
	Oprelvekin/IL-11	IL-11	Recombinant human cytokine	Phase 1/2
	Lactococcus lactis	IL-10	Living nonpathogenic microorganisms expressing IL-10	Phase 1/2
Blocking cell recruitment	Alicaforsen	Endothelial ICAM-1	Phosphorothioate-modified antisense oligodesoxynucleotide	Phase 3
	CCX282-B	Antichemokine receptor CCR9	Small molecule	Phase 3
	Vedolizumab (MLN-0002)	Leukocyte $\alpha_4\beta_7$ integrin	Humanized mAb	Phase 3
Enhancing repair	Teduglutide	Intestinal GLP-2 receptors	Analogue of human peptide GLP-2	Phase 2
	Somatropin	Intestinal epithelium	GH peptide	Phase 2
Innate immune stimulation	Sargramostim	Intestinal epithelium, neutrophils, monocytes	Yeast-derived recombinant human GM-CSF	Phase 3
	Filgrastim	Neutrophils	*E. coli*-derived human (G-CSF)	Phase 1/2
Induction of oral tolerance	complex of autologous colon-derived antigens	Induction of oral tolerance	Autologous colonic extracts	Phase 1/2
	Opebacan	Induction of oral tolerance	Autologous colon-derived antigens	Phase 1/2

GLP-2, glucagon-like peptide-2; IL, interleukin; mAb, monoclonal antibody; MAP, mitogen-activated protein; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; GCSF, granulocyte colony-stimulating factor; TNF, tumor necrosis factor

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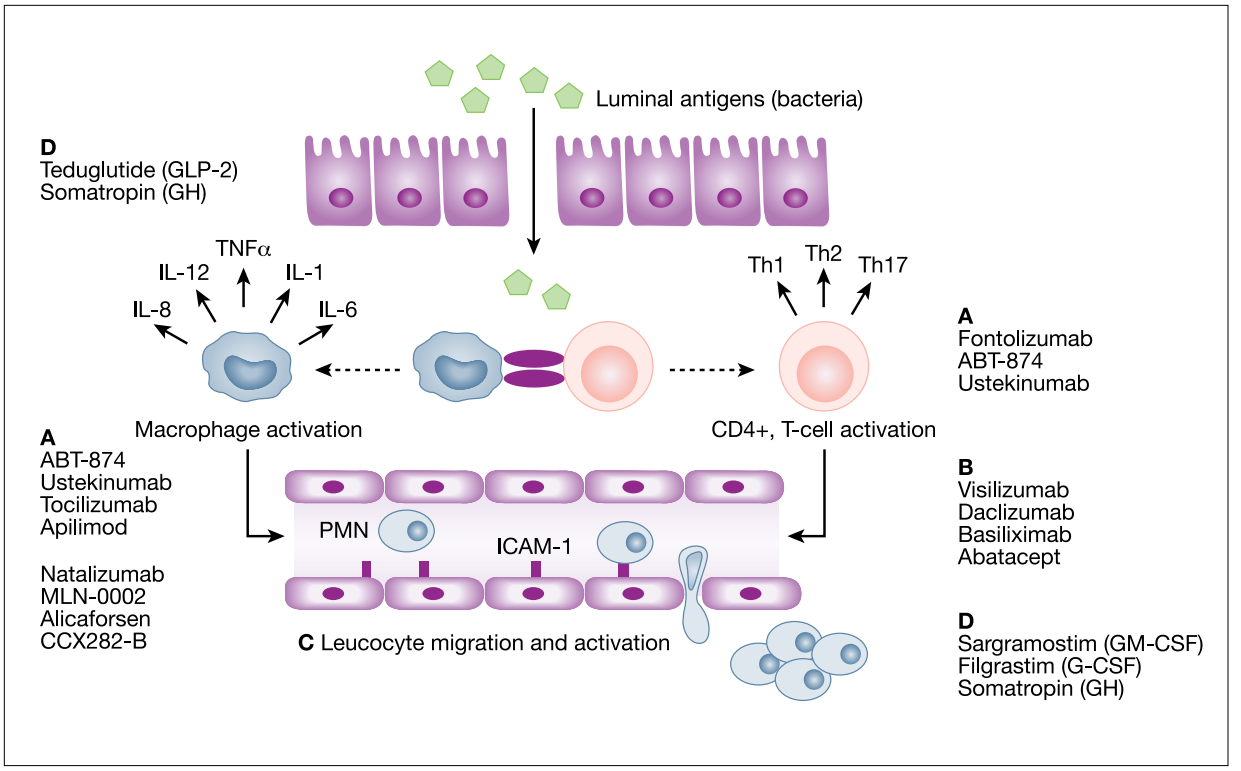

Figure 2. Overview of therapeutic targets in CD.[1] A) Cytokine therapies; B) T-cell blocking agents; C) Antiadhesion molecules; and D) Growth factors.

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provides an overview of the therapeutic targets of investigational biologics. Therapeutic attempts to block specific subsets of T cells include visilizumab, a monoclonal antibody directed against the CD3 chain of the T-cell receptor, and cM-T412, which blocks CD4+ T-cells.[1] Other molecules such as IL-10 attempt to modulate regulatory T-cell function and control the inflammatory process directed by other T-helper cells.

Another approach is to block cytokines and molecules involved in T-cell differentiation and activation with such varied agents as fontolizumab, a humanized antibody directed at interferon □; tocilizumab, targeted at the IL-6 receptor; and abatacept, a soluble recombinant fusion protein that blocks CD28 and is approved for rheumatoid arthritis.[1,37] Additionally, there is increasing interest in the development of agents that target the IL-12/IL-23 pathways, as well as the IL-17/IL-23 pathways. Dr. Targan noted that preliminary data with compounds that target the p40 subunit on the IL-12 and IL-23 cytokines have suggested that there may be a subpopulation of CD patients who will respond to this approach.

Adhesion molecule inhibitors aim to block trafficking of leukocytes from the bloodstream to sites of inflammation. Like natalizumab, the investigational agent vedolizumab (MLN0002) is a humanized monoclonal antibody that acts as a selective adhesion molecule (SAM) inhibitor but differs from natalizumab in that vedolizumab has increased specificity for □$_4$□$_7$ integrin.[36] Dr. Plevy explained, "□$_4$□$_7$ integrin inhibitors will only keep inflammatory cells out of the gut," which may confer a superior safety profile in comparison to less selective agents.[36] Alicaforsen is a human antisense oligonucleotide that blocks expression of intercellular adhesion molecule-1 (ICAM-1) by disabling target RNA molecules and blocking the translation of protein.[38,39] ICAM-1 plays an important role in leukocyte adhesion and migration and local lymphocyte stimulation, and it is responsible for T-lymphocyte trafficking in the intestine.[39] The compound CCX282-B, an oral agent, uses an alternative approach by binding to chemokine receptor 9 (CCR9), which recruits cells into the epithelium of the small intestine.[1]

Additional investigational approaches to IBD therapy include compounds that enhance repair of the intestinal epithelium (teduglutide, somatropin), growth factors that stimulate the innate immune system (sargramostim, filgrastim), and autologous colonic extracts designed to induce oral tolerance to the intestinal bacterial flora.[1] Although in varying stages of clinical development, some of the investigational biologic agents have demonstrated promising preliminary results in IBD patients.[1,36] Dr. Targan speculated that these investigational molecules "potentially have an effect that may be dramatic in a subpopulation of patients." However, Dr. Targan also explained that "the definability of that population is going to be a critically important determinant of whether the compound is moved forward in development."

Biologic Therapeutic Options for IBD

The Evolution of Treatment Goals for IBD

Historically, the predominant treatment goals for IBD were to eliminate symptoms with as few side effects and long-term sequelae as possible.[40] Traditionally, composite disease activity indices such as the Crohn's Disease Activity Index (CDAI) have been used to evaluate disease activity, with a drop of 70 or 100 points generally indicating a successful response to therapy.[41] However, as Dr. Sands pointed out, "patients may have diarrhea. They may have abdominal pain. They may not feel well, and yet you may look in with a colonoscope and find that there is, in fact, no identifiable inflammation." Given the lack of consistent correlation with clinical symptoms and mucosal healing, "studies and clinicians are increasingly turning to bona fide evidence that inflammation is present and that inflammation has resolved after a new treatment is begun." Moreover, with the growing emphasis on therapeutic strategies that can alter the natural history of disease, current treatment goals for IBD are evolving to include the induction and maintenance of endoscopic healing.[42-45]

Although the ability of various therapies to heal the mucosa has been documented in both CD and UC,[42,44-46] data demonstrating the clinical relevance of mucosal healing are just beginning to emerge. Recently, Frøslie et al found that mucosal healing was associated with less inflammation after 5 years (P=0.02) and decreased need for steroid treatment at 5 years (P=0.02) among 141 CD patients, as well as lower risk of future colectomy among UC patients (P=0.02).[42] Mucosal healing has also been associated with other clinical outcomes, such as a trend towards fewer hospitalizations among CD patients who achieved endoscopic remission with infliximab in the ACCENT 1 trial.[46]

Citing the results of a recent trial comparing the impact of early combined immunosuppression in early CD (ie, top-down therapy),[45] Dr. Sands noted that the effect of mucosal healing "seems to be even more powerful in patients with relatively newly diagnosed CD." In this 2-year, open-label trial, newly diagnosed CD patients who received early combined immunosuppression with azathioprine (AZA) and infliximab-induction therapy achieved superior endoscopic improvement at 104 weeks compared with those who received conventional treatment with corticosteroids followed in sequence by AZA and infliximab.[45] Patients receiving early combined immunosuppression achieved more rapid clinical remission, more rapid improvement in quality of life, and lower corticosteroid use compared with those receiving conventional treatment. In addition, mucosal healing was significantly more common at year 2 with early combined immunosuppression. Dr. Sands concluded that "we are coming to believe that mucosal healing will be a good surrogate for improvement of ultimate outcome of the diseases, but that connection still has to be better established."

Other evolving treatment goals for IBD disease include corticosteroid sparing, improved patient quality of life, and reduction of hospitalizations and surgeries.[40] Given the considerable morbidity and increasingly recognized risk of mortality associated with corticosteroid therapy,[28,45,47] the ability of an agent to facilitate steroid discontinuation or dose reduction represents an important advantage in medical therapy for IBD. Frequently measured by the Inflammatory Bowel Disease Questionnaire (IBDQ), health-related quality of life (HRQoL) is often included as a secondary end point in clinical studies in CD and UC patients.[48-51] Such measures can not only complement clinical disease activity indices, but also can provide a more comprehensive perspective on the impact of a therapy on a patient's overall well-being.[48] Additionally, recent analysis of a medical and pharmacy claims database from approximately 20,000 IBD patients in the United States confirmed the significant contribution of hospitalization to IBD-related costs, accounting for 31% and 38% of annual costs of CD and UC, respectively.[52] Accordingly, reducing surgeries and hospitalization is an important goal of therapy. Dr. Sands added that "therapies that can decrease hospitalizations and surgeries will likely prove to be cost-effective."

Clinical Efficacy and Safety of Current Biologic Agents

Randomized controlled trials have demonstrated the efficacy of all four of the approved biologic agents (infliximab, adalimumab, certolizumab pegol, and natalizumab) in inducing and maintaining remission in

CD.[30,53-58] Infliximab has proven to be effective for inducing and maintaining remission in patients with UC, as well.[44] Other data support the ability of biologic agents to achieve fistula healing in CD[59] and significantly reduce corticosteroid use.[53,56] Significant improvements in HRQoL have been demonstrated in IBD patients who received infliximab,[49] certolizumab pegol,[51] and natalizumab.[50,57] Moreover, published subset analyses and preliminary data support the ability of the anti-TNF agents[60] and natalizumab[61] to reduce hospitalization and surgeries in patients with CD. Although conventional agents are generally effective at inducing remission in active disease and some (ie, immunomodulators) appear to be steroid sparing,[62,63] Dr. Plevy summarized, "the data that seem to be unique to the biologics is the degree of mucosal healing that we're seeing, the closure of fistulas with the anti-TNF agents, and the potential ability to prevent hospitalizations and surgeries."

Despite the potential benefits of biologic agents, particularly for patients who are likely to have aggressive disease, the use of these agents must be weighed against their potential toxicities. All anti-TNF therapies have been associated with a broad range of infections, including tuberculosis and opportunistic infections.[64] In a regression analysis of 100 consecutive IBD patients at Mayo Clinic, Toruner et al found that any use of corticosteroids, AZA/6-MP, and infliximab significantly increased the odds for opportunistic infection compared to no use of these drugs (P<0.001).[47] The use of infliximab alone increased the risk of opportunistic infection by a factor of 11 (OR 11.1; 95% CI 0.8–148; P<0.001), and the risk increased significantly when used in combination with other immunosuppressive agents. Commenting on this finding, Dr. Plevy added that "it may be combined immunosuppressive therapy, combinations of immunomodulators with biologics, and even the addition of steroids on top of that that may be markers for risk of opportunistic infections."

Another area of concern with the biologic agents is neoplasia, and, in particular, the risk of lymphoma. A recent meta-analysis of 26 studies involving 8,905 CD patients indicated a significantly elevated risk of non-Hodgkin's lymphoma (standardized incidence ratio [SIR] = 3.23, 95% CI: 1.5–6.9) among patients treated with anti-TNF agents. Although this increased risk was statistically significant when compared with the general population, the absolute risk was small (6.1 per 10,000 patient-years). The authors concluded that the risk in using anti-TNF agents with immunomodulators should be weighed against the benefits of treatment in this population, and that further prospective data are needed for a more accurate assessment of risk.[65] The association with malignancy was highlighted by the results of a meta-analysis of nine trials involving 3,493 rheumatoid arthritis patients that demonstrated a significant dose-dependent increased risk of malignancy in patients treated with infliximab or adalimumab (pooled OR for malignancy, 3.3; 95% CI, 1.2–9.1).[66]

A particularly concerning risk unique to the blockade of □4-integrins by natalizumab is the development of progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the JC virus that is generally debilitating or fatal.[67] In clinical trials of natalizumab involving nearly 3,400 patients with multiple sclerosis or CD, PML occurred in 3 patients, all of whom were receiving recent or concomitant immunosuppressive therapy.[36,67] Two new cases of PML, both of which occurred in multiple sclerosis patients receiving natalizumab monotherapy, have been reported subsequent to natalizumab approval in 2008.[68] Although the mechanism for natalizumab-associated PML remains unknown, it has been proposed that natalizumab mobilizes JC-virus–infected lymphocytes from endogenous bone marrow, resulting in uncontrolled viral replication.[36] Natalizumab may also compromise central nervous system immune surveillance by inhibiting lymphocyte trafficking to the brain. Dr. Plevy discussed the significance of this by explaining "natalizumab blocks the brain from accessing inflammatory cells that may actually combat this viral infection." However, he added "because the investigational selective anti-adhesion molecule vedolizumab is directed against only $\square_4\square_7$ integrins, this antibody will keep inflammatory cells only out of the gut. Therefore, at least in theory, it is possible that there may not be an association of vedolizumab with PML."

Positioning Future Biologic Therapies in IBD Treatment Strategies

In contrast to the traditional step-up approach to IBD therapy in which therapy is sequentially aimed to the severity of the disease,[64] early intervention with biologic therapies (ie, top-down therapy) has been purported to improve outcomes and even alter the natural history of disease. Indeed, results of the top-down-vs-step-up trial reported by D'Haens et al suggested that patients receiving early combined immunosuppression with infliximab-induction therapy achieved more rapid remission, more sustained mucosal healing, and reduction in steroid exposure.[45]

Given the potential risks associated with biologic therapies, however, the ability to identify patients with aggressive disease who may progress rapidly to complications and/or surgery is essential to selecting appropriate candidates for early intervention with biologic agents. Dr. Targan agreed that a more targeted approach of using various predictors—whether "at a genomic level, a physi-

ologic level, and/or a clinical level"—will be critical in identifying the patient population who may respond to biologic therapies. "We're going to treat earlier for those patients who we know are going to have aggressive disease, and try to target the appropriate therapies to those patients whose pathways are going to be best affected by these therapeutics."

Finally, appropriate risk assessment and mitigation strategies are key factors in determining the role of biologic agents in the IBD treatment paradigm and in developing new therapies. Difficulties in assessing risks for these agents include lack of precision in determining risks for a particular agent and discordance between patients and physicians regarding those risks. Patients with IBD may underestimate the risks of treatment with biologic therapies,[69] despite over half of the respondents recalling discussing the risks and benefits of their therapy with their physician.[69] Nonetheless, patients with CD have indicated that they are willing to accept some increased risks of serious adverse events in exchange for clinical efficacy, with symptom severity an important driver of the level of acceptable risk.[70] Dr. Sands concluded that "the first thing is to be able to pin down exactly what the risks are, and possibly even personalize those risks for an individual of a certain age or gender, or one who may have genetically some risk factor that predisposes him or her to one complication of treatment or another."

Conclusions

IBD is a chronic, destructive, inflammatory disorder that results from the interaction of a dysregulated mucosal immune response to intestinal microbacteria in genetically susceptible individuals. The recent identification of at least 30 different susceptibility loci for CD has highlighted the importance of the innate immune system in the initiation of disease. The adaptive immune system plays a central role in propagating intestinal inflammation; understanding of the role played by environmental factors continues to evolve.

The IBDs are chronic disorders characterized by a heterogeneous clinical presentation and disease course. CD is typically a progressive and destructive disorder, with most patients eventually developing a stricturing or penetrating complication requiring one, if not multiple, surgeries. Factors that may help predict patients that will develop early aggressive disease include age under 40 years, perianal disease at diagnosis, and ileocolonic location.

Currently available biologic agents include the anti-TNF agents (infliximab, adalimumab, certolizumab pegol), whose myriad effects include binding circulating TNF and inducing apoptosis, and the anti-adhesion molecule natalizumab, which disrupts the trafficking of inflammatory cells to the bowel. A number of biologic agents are under development for IBD, most of which target events downstream of the inflammatory cascade rather than the disease itself. Many investigational biologics are aimed at inhibiting T-cell function, blocking T-cell proinflammatory cytokines, or inducing apoptosis of T cells or a subset of these cells. By targeting integrins specific to the gut, investigational anti-adhesion molecules offer more selective gastrointestinal restriction of lymphocyte trafficking than natalizumab. Other investigational approaches include compounds that enhance repair of the intestinal epithelium and growth factors that stimulate the innate immune system.

Although the treatment goals for IBD have historically focused on the induction and maintenance of remission, current goals are evolving to include mucosal healing, improved quality of life, and reduction in surgeries and hospitalizations. With the introduction of biologic therapies for IBD over the last decade, researchers are increasingly able to realize these treatment goals and hopefully alter the natural history of disease. Current biologic agents not only effectively induce and maintain remission in CD, but also have demonstrated efficacy in healing fistulas, achieving mucosal healing, improving quality of life, and reducing surgeries and hospitalizations. Despite these benefits, careful risk-benefit assessment and targeted patient selection will remain key factors in the appropriate use of these agents in the IBD population. "We're now a decade into the advent of biologic therapies" noted Dr. Stephen Hanauer, "and on the cusp of a number of new treatments that hopefully are going to improve the therapeutic ratio for our patients and ultimately reduce the disease burden on a long-term basis." The future of biologic therapy for IBD will likely evolve as understanding of the pathogenesis of the disease advances, allowing patients to be stratified into distinct subgroups and therapies individualized for a more predictable response and more favorable therapeutic outcomes.

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Therapeutic Targets for Emerging Biologic Therapies in IBD

CME Posttest:

1. Which of the following have been implicated in the pathogenesis of inflammatory bowel disease (IBD)?
   a. Activation of the adaptive immune system
   b. Defects in the intestinal epithelium
   c. Imbalance between protective and harmful intestinal bacteria
   d. All of the above

2. Which of the following regarding the natural history of IBD is/are true?
   a. Early mesalamine use is associated with a complicated disease course
   b. Most patients with Crohn's disease will require surgery within 15 years of diagnosis
   c. Most patients with Crohn's disease will require therapy with corticosteroids
   d. All of the above

3. The mechanism of action of the anti–tumor necrosis factor (TNF) agents is completely understood.
   a. True
   b. False

4. Which of the following statements regarding the mechanism of current biologic agents used in IBD is/are true?
   a. Apoptosis is the only mechanism of action responsible for the benefit of the anti-TNF agents in IBD
   b. Certolizumab pegol, but not infliximab, induces apoptosis in immune cells
   c. The anti-adhesion molecules limit trafficking of inflammatory cells into the bowel
   d. All of the above

5. Current biologic agents have demonstrated efficacy in
   a. Healing fistulas in Crohn's disease
   b. Inducing and maintaining remission in Crohn's disease and ulcerative colitis
   c. Improving quality of life in Crohn's disease and ulcerative colitis
   d. All of the above

6. Which of the following statements regarding the use of biologic agents in IBD is/are true?
   a. Initiating biologic agents early in the disease course may improve outcomes for some patients with Crohn's disease
   b. The potential risks of biologics clearly outweigh the benefits for IBD patients at risk of aggressive or complicated disease
   c. The use of biologic agents has been shown to increase overall healthcare costs related to IBD
   d. All of the above

7. Potential toxicities of the current biologic agents include
   a. Lymphoma
   b. Opportunistic infections
   c. Progressive multifocal leukoencephalopathy
   d. All of the above

8. Which of the following represent investigational therapeutic strategies for treating IBD?
   a. Blocking T-cell differentiation and activation
   b. Enhancing intestinal epithelial repair
   c. Inhibiting T-cell function
   d. All of the above

9. Evolving treatment goals for IBD include
   a. Corticosteroid sparing
   b. Improved patient quality of life
   c. Reduction of hospitalizations and surgeries
   d. All of the above

10. Key strategies for positioning biologic agents in future IBD treatment paradigms will likely include
    a. Careful risk-benefit assessment
    b. Identifying subpopulations of patients who are likely to respond to these agents
    c. Introducing biologic agents early in the disease course in patients who are likely to have aggressive disease
    d. All of the above

Activity Evaluation Form: Therapeutic Targets for Emerging Biologic Therapies in IBD

Release date: July 2009 **Expiration date:** July 31, 2010
Participants requesting credit must read and review the CME activity. A certificate will be issued only upon receipt of a completed activity posttest with a score of 70% or better, along with a completed evaluation and certificate information form.

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Fax: (610) 363-7410
If you mail or fax your completed posttest, evaluation, and certificate information form, your certificate will be sent to you in approximately 4 to 6 weeks.

CERTIFICATE INFORMATION

Please complete to receive credit for this program. Please print clearly.

Name _____ Degree _____

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Organization _____

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City _____ State/Country _____ Postal Code_____

E-mail _____

Please check one: ❒ Physician ❒ Non-Physician I claim _____ *AMA PRA Category 1 Credits™* <up to 1.25 credits>.

Signature_____

❒ I would like to receive information about future educational activities on the topic of biologics in the treatment of IBD.

Posttest answers: Please fill in your answers to the right: 1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10____

EVALUATION

1. Rate the extent to which you agree or disagree.	***Strongly Agree***				***Strongly Disagree***
• I am satisfied with the overall quality of this activity	5	4	3	2	1
• Participation in this activity changed my knowledge/attitudes	5	4	3	2	1
• I will make a change in my practice as a result of participation in this activity	5	4	3	2	1
• The activity presented scientifically rigorous, unbiased, and balanced information	5	4	3	2	1

Please list the changes you plan on making in your practice as a result of your participation in this activity:

_____

If you felt the activity was biased, please explain:

_____

2. This activity helped me to achieve the following objectives:	***Strongly Agree***				***Strongly Disagree***
• Describe the mechanisms of action of existing and novel biologic agents used in the treatment of IBD	5	4	3	2	1
• Compare and contrast how different biologics target unique aspects of the inflammatory cascade	5	4	3	2	1
• Evaluate the clinical efficacy and safety of current biologic therapeutic options for the management of IBD	5	4	3	2	1
• Summarize the therapeutic need for the novel biologic therapeutic options under development, as well as their potential efficacy and risks	5	4	3	2	1

If you felt the learning objectives were not met, please explain:

_____

3. What information remains unclear? _____

4. Questions or comments regarding this activity: _____

_____

5. How did you hear about this activity? (Please check all that apply) ❒ Direct mailing ❒ Curatio Web site ❒ Colleague ❒ E-mail ❒ Other (Please specify.)_____

6. Time spent completing this activity? ❒ <.5 hr ❒ 5–1.0 hrs ❒ 1.0–1.25 hrs ❒ >1.25 hrs

7. Suggested topics and/or speakers you would like for future programs: _____

_____

8. What is/are your preferred format(s) for earning continuing medical education credits? (Please check all that apply.)
❒ Satellite symposium ❒ Grand rounds ❒ CD-ROM ❒ Dinner meeting ❒ Internet activity ❒ Podcast
❒ Teleconference ❒ Journal supplement ❒ Newsletter/monograph ❒ Other (Please specify.) _____

Thank you for taking time to complete this evaluation.