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Targeting Leukocyte Trafficking for the Treatment of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory disease of the intestine that includes both Crohn's disease and ulcerative colitis, and afflicts nearly 1 million people throughout North America. As our understanding of IBD pathogenesis grows, several new therapies have been developed that use monoclonal antibodies to specifically target key mediators and biological pathways implicated in IBD immune dysfunction. One important pathway involves leukocyte trafficking and infiltration into the affected intestinal tissues. This review provides a summary of the different therapies that have been developed to inhibit leukocyte trafficking to the inflamed gut, and evaluates the relative safety and efficacy of these novel drugs within the context of existing medical therapies for IBD.

THE TARGETED APPROACH TO IBD THERAPY

The development of novel potential therapies for the treatment of inflammatory bowel disease (IBD) has burgeoned over the past two decades as new advances in our understanding of the immune mechanisms underlying IBD pathogenesis are effectively translated into development of more targeted “smart bomb” approaches to treatment. IBD is a chronic inflammatory disease of the gut that encompasses both Crohn's disease (CD) and ulcerative colitis (UC). Medical management of IBD was long dominated by the use of broad-spectrum corticosteroids to suppress the immune system systemically, thus indirectly improving chronic intestinal inflammation. Lacking a clear understanding of the specific gut immune pathways implicated in the disease, as well as the role played by genetic and environmental factors, this generalized approach to immunosuppression represented the main medical strategy for avoiding surgical resection. Unfortunately, corticosteroids are associated with a wide range of debilitating side effects, and a proportion of patients either do not respond to steroids or relapse as they begin to taper their dose. Over the past two decades, these limitations have driven a significant research effort focused on developing new strategies for IBD therapy to provide a high level of efficacy without the associated side effects inherent in broad-spectrum immunosuppression.

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CONFLICT OF INTEREST

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The model for this targeted approach came with the introduction of a new class of monoclonal antibody (mAb)-based drugs that specifically inhibit mediators of intestinal inflammation in IBD. The first success for this approach was infliximab, an infusion-based chimeric mAb that targets tumor necrosis factor (TNF)- α , a key proinflammatory cytokine within the inflamed intestinal mucosa. Initial clinical trials revealed a clinical response rate greater than 60% in patients with moderate to severely active CD and UC, along with an acceptable safety profile that included some risk of infusion and delayed hypersensitivity reactions, infections, and a questionable small increased risk of lymphoma.^{1–4} Infliximab received US Food and Drug Administration (FDA) approval for CD in 1999. Since this time, three additional anti-TNF drugs have reached the market with similar efficacy and safety profiles (adalimumab, certolizumab pegol, and golimumab). TNF inhibition has revolutionized treatment for IBD, significantly reducing the need for hospitalizations and surgeries,⁵ and has provided a strong precedent for the development of more targeted therapeutics aimed at other important biological pathways underlying IBD pathogenesis.

The role of leukocyte trafficking in IBD pathogenesis

IBD is characterized by a massive infiltration of circulating leukocytes into the inflamed intestinal mucosa. Naive circulating T cells encounter antigen within Peyer's patches located throughout the intestine and take on an effector/memory phenotype. These effector-primed T cells then enter the circulation and home back to the gut. One key biological pathway that mediates the onset of chronic intestinal inflammation during IBD is the complex set of interactions that occur between circulating leukocytes and intestinal vascular endothelial cells to allow migration of the leukocyte across the endothelium and into the intestinal mucosa.⁶

Leukocyte adhesion and extravasation across the intestinal endothelium involves a multistep process whereby circulating immune cells are captured, roll, undergo activation, firmly adhere, and finally transmigrate into the damaged tissue (**Figure 1**). Selectins located on the surface of intestinal endothelial cells form low-affinity bonds with sialyl Lewis^X-modified glycoproteins on circulating leukocytes by rapidly altering the conformation of their binding domain between an open and closed state. These low-affinity bonds create a rolling effect that slows the circulating leukocyte and allows the cell to begin to adhere to the endothelium. Full adhesion is mediated by the stable binding of integrin receptor molecules located on the leukocyte to inducible cellular adhesion molecules ligands, which are expressed on the surface of the intestinal endothelial cell during acute and chronic inflammation. Chemokines are also induced on endothelial cells within the context of inflammation, and act as potent chemoattractants for their cognate receptors on the rolling leukocytes to promote their activation and migration across the endothelium.⁷

Integrin-adhesion molecule interactions

Integrins are heterodimeric receptors expressed on the surface of circulating leukocytes that are composed of both an α and β subunit. Each subunit is a class-I transmembrane protein with a small (40–70 amino acid) cytoplasmic domain and much larger extracellular domain. Several forms of the α and β subunits exist, and they join together in various combinations of integrin molecules expressed on human leukocytes. These combinations can be specific to

a particular type of leukocyte, or can determine the target tissue for leukocyte trafficking. For example, the CD11c/CD18 ($\alpha_x\beta_2$) integrin is considered a marker for monocytes and neutrophils, while CD11a/CD18 ($\alpha_1\beta_2$ or LFA-1) is specific to T-lymphocytes; $\alpha_4\beta_7$ is a marker for specific leukocyte trafficking to the intestine, a property that is particularly important for IBD therapies that target leukocyte trafficking to the inflamed gut (**Table 1**).

The natural integrin ligands are cellular adhesion molecules (CAMs), which are members of the immunoglobulin superfamily expressed on the surface of vascular endothelial cells. In particular, three CAMs are known to play a role in leukocyte trafficking to the inflamed intestine during active phases of IBD. Intracellular adhesion molecule (ICAM)-1 (CD54) is constitutively expressed at low levels on the surface of intestinal endothelial cells, and is induced upon exposure to proinflammatory cytokines during inflammation. By binding to its receptor, the CD11a/CD18 integrin ($\alpha_L\beta_2$, or LFA-1) on circulating leukocytes, ICAM-1 causes firm adhesion, activation, and migration of the leukocyte into the inflamed mucosa. Mucosal addressin cellular adhesion molecule (MadCAM)-1 is expressed on vascular endothelial cells within the Peyer's patches and intestinal lymphoid tissues and binds to the $\alpha_4\beta_7$ integrin receptor to regulate specific homing of memory/effector T cells to the intestine. Finally, vascular cell adhesion molecule (VCAM)-1 (CD106) is transiently expressed upon exposure to cytokines, and binds to one of its two natural integrin ligands, $\alpha_4\beta_1$ or $\alpha_4\beta_7$. The $\alpha_4\beta_1$ integrin (VLA-1) primarily mediates leukocyte trafficking to the central nervous system (CNS), while $\alpha_4\beta_7$ mediates homing to the gut. Several lines of evidence suggest a clear role for CAMs in IBD pathogenesis, making blockade of the integrin-cellular adhesion molecule pathway within the gut-associated lymphoid tissues an attractive strategy for IBD drug development. Several new therapies have been explored and are summarized in **Figure 2**.

Targeting the ICAM-1/LFA-1 interaction

ICAM-1 was the first intestinal CAM to be investigated as a specific target for therapeutic intervention in IBD. Early studies revealed that ICAM-1 expression was induced in areas of active inflammation within the intestinal mucosa of patients with both CD and UC,⁸ and multiple antibody blocking studies of ICAM-1 in rodent models of chemically induced colitis showed that ICAM-1 inhibition caused amelioration of experimental colitis.^{9–11} Moreover, mice deficient in ICAM-1 and treated with dextran sodium sulfate (DSS) enemas to chemically induce colitis exhibited significantly less inflammation and a reduced inflammatory infiltrate within the mucosal lamina propria compared with wildtype mice.¹² These studies provided strong evidence that ICAM-1 may contribute to IBD pathogenesis.

Alicaforsen (ISIS 2302)—In the late 1990s it was reported that pre-treatment of DSS colitic mice with a murine-specific antisense ICAM-1 oligonucleotide (ISIS 3082) caused an improvement in the clinical signs of colitis in a dose-dependent manner, as well as reduced numbers of leukocytes within the colonic mucosa, with no signs of toxicity at pharmacologically relevant doses.¹³ These results provided proof of concept for the subsequent development of a human antisense inhibitor of ICAM-1 by ISIS Pharmaceuticals (Alicaforsen, ISIS 2302) for the treatment of CD. The drug used RNase H to reduce mRNA expression levels of the ICAM-1 gene, thus inhibiting its function in leukocyte recruitment.

Although the drug was found to be safe, multiple clinical trials could not demonstrate efficacy in patients with mild to moderate steroid-refractory or steroid-dependent CD compared to placebo, and drug development was suspended in December 1999.^{14–16}

However, alicaforsen was revisited when an enema formulation was developed to deliver the oligonucleotide directly to the affected colons of UC patients. An initial phase II randomized, double-blind, placebo-controlled trial evaluated the enema formulation in 40 patients with mild to moderate distal UC. The results showed that the enema formulation was effective in a dose-dependent manner and was well tolerated by patients.¹⁷ A subsequent, larger multicenter study evaluated the safety and efficacy of two doses of alicaforsen enema compared to standard mesalamine enema.¹⁸ In all, 190 patients were randomized to receive nightly enemas of 120 mg alicaforsen, 240 mg alicaforsen, or 4g mesalamine. No differences were observed in 6-week response rates between the three groups (mesalamine = 50%, alicaforsen 120 mg = 40% and 240 mg = 41%, $P = 0.27$ and 0.32 , vs. placebo). However, the percentage of patients experiencing clinical remission was higher in treated patients, suggesting that the drug had comparable induction efficacy to mesalamine, but may in fact produce a more durable response. Similar results were obtained from a phase II double-blind, placebo-controlled study in acute mild to moderate left-sided UC, where again, no differences were observed in clinical response between groups, but patients receiving 240 mg alicaforsen daily had a significantly lower rate of relapse compared to placebo.¹⁹

Alicaforsen has also been tested in patients suffering from chronic, unremitting pouchitis. In an open-label study of 12 patients, alicaforsen enema induced a significant reduction in Pouchitis Disease Activity Index (PDAI) scores from baseline after 6 weeks of treatment. In addition, 58% of patients achieved a clinical remission (7/12 patients) and 10 of 12 patients achieved endoscopic mucosal appearance scores of 0 or 1.²⁰ Based on these findings, alicaforsen enema may be an effective treatment for patients with chronic pouchitis, although further studies are warranted.

Efalizumab (Raptiva)—Efalizumab is a humanized anti-CD11a mAb that was initially developed by Genentech (South San Francisco, CA) for treatment of psoriasis. By binding to CD11a (the α_L integrin), the drug inhibits the binding of ICAM-1 to its receptor, LFA-1 ($\alpha_L\beta_2$), on the surface of circulating lymphocytes. After demonstrating efficacy and safety in clinical trials for psoriasis, efalizumab was approved in 2003 for this indication. Based on the role of LFA-1/ICAM-1 in lymphocyte activation and trafficking to the gut, a small open-label study was subsequently performed to evaluate the efficacy and safety of efalizumab in 15 patients with moderate to severely active CD.²¹ By 8 weeks of treatment, 10 patients achieved clinical response (67%), and six patients achieved clinical remission (40%). No serious adverse events were reported. However, despite this promising early result efalizumab was voluntarily withdrawn from the US market in 2009 after three reported cases of progressive multifocal leukoencephalopathy (PML) in psoriasis patients. PML is a rare and usually fatal neurological condition caused by the JC polyoma virus that occurs exclusively in immunocompromised patients who have lost the ability to suppress the normally contained JC virus. Analysis of the peripheral blood and cerebral spinal fluid from two patients with severe psoriasis who died of PML after being treated for at least 3 years

with efalizumab revealed that both patients had reduced transendothelial migration of lymphocytes *in vitro* and decreased activation of CD8⁺ T cells.²² These data suggest that LFA-1 plays a critical role in control of JC virus under normal conditions, and that inhibition of the α_L integrin through mAb therapy impacts recruitment of leukocytes to the CNS that are important for maintaining homeostatic control over the virus. The occurrence of PML has been a recurring serious concern with biological therapies that inhibit leukocyte trafficking to the CNS.

Targeting the MAdCAM-1/ $\alpha_4\beta_7$ interaction

Early animal studies in the cotton-top tamarin model of acute colitis demonstrated that mAb blockade of the α_4 integrin, which inhibits both $\alpha_4\beta_1$, the integrin receptor for VCAM-1, and $\alpha_4\beta_7$, the gut-specific integrin receptor for MAdCAM-1, attenuated tamarin colitis.²³ Additional animal studies in the CD45RB^{hi} T-cell transfer model of murine colitis showed that blocking mAbs against both the β_7 integrin and MAdCAM-1 inhibited the recruitment of lymphocytes to the intestine in recipient SCID mice and significantly decreased the severity of their chronic intestinal inflammation.²⁴ Interestingly, this effect was not observed with anti-VCAM-1 and anti-ICAM-1 mAb treatment in this model.²⁵ Similar ameliorating effects were observed with MAdCAM-1 inhibition in several other animal models of experimental colitis.^{26–28} In humans, MAdCAM-1 is constitutively expressed under normal conditions on human endothelial cells that line the intestinal lamina propria, and is upregulated at sites of inflammation in patients with CD and UC.²⁹ Radiolabeled mAb studies revealed that intestinal MAdCAM-1 expression in mice is enhanced within 18 hours of systemic TNF- α administration, and remains upregulated for 48 hours postadministration.³⁰ In addition, colitogenic IL-10 deficient mice experienced a 4–5-fold increase in MAdCAM-1 expression within the colon after systemic TNF- α administration compared to control mice. Based on these findings, the MAdCAM-1/ $\alpha_4\beta_7$ interaction has been a promising target for emerging biological therapies that disrupt leukocyte trafficking specifically to the gut.

Natalizumab (Antegren or Tysabri)—Natalizumab is a humanized anti- α_4 mAb originally developed by Elan Pharmaceuticals (Dublin, Ireland) and Biogen Idec (Cambridge, MA) for treatment of multiple sclerosis. Natalizumab inhibits the biological activity of both $\alpha_4\beta_1$, which mediates lymphocyte homing primarily to the CNS, as well as $\alpha_4\beta_7$, which is expressed specifically on memory/effector T lymphocytes bound for the inflamed intestine. In 2003, a phase II clinical trial conducted in 248 patients with moderate to severely active CD showed that patients randomized to receive two infusions of either 3 mg/kg or 6 mg/kg of natalizumab had higher rates of clinical response and remission at multiple timepoints compared to placebo-treated patients, with similar rates of adverse events occurring between the groups.³¹ In 2004, natalizumab was approved by the FDA for the treatment of multiple sclerosis. The following year, two large-scale phase III clinical trials for CD were reported evaluating the efficacy of natalizumab in both induction of clinical response or remission (ENACT-1), as well as maintenance of response or remission (ENACT-2).³² In the ENACT-1 trial, 948 patients with moderate to severely active CD were randomized to receive 3 mg/kg of natalizumab infusion or placebo at 0, 4, and 8 weeks, and the primary endpoint was a 70-point reduction in the CD Activity Index (CDAI) at 10

weeks; in ENACT-2, 339 patients who initially responded to natalizumab infusion during ENACT-1 were rerandomized to receive 3 mg/kg natalizumab or placebo every 4 weeks through week 56, and the primary endpoint was percent of patients with a sustained clinical response through week 36. The results showed that patients treated with natalizumab and placebo had similar clinical response and remission rates at week 10 (clinical response: 56% vs. 49%, $P = 0.05$; clinical remission: 37% vs. 30%, $P = 0.12$). Among those patients who did respond to natalizumab, continuous treatment every 4 weeks was associated with a much higher probability of sustained response through 36 weeks (61% vs. 28%, $P < 0.001$). Interestingly, subgroup analysis revealed that ENACT-1 patients with baseline C-reactive protein (CRP) levels above the upper level of normal (>2.87 mg/L) had significantly higher week-10 clinical response and remission rates. Based on this observation, the ENCORE trial was designed to evaluate the efficacy in this population.³³ Similar to ENACT-1, 509 patients were randomized to receive either 3 mg/kg of natalizumab infusion or placebo at 0, 4, and 8 weeks, and the primary endpoint was a 70-point reduction in CDAI from baseline at 8 and 12 weeks. The study revealed that 48% of natalizumab-treated patients responded by 8 weeks and sustained their response through 12 weeks, compared to 32% of patients receiving placebo ($P < 0.001$); significant differences were also seen in clinical remission rates (26% vs. 16%, $P = 0.002$). The incidence of persistent antibodies associated with natalizumab in clinical trials for CD was 6%, which was associated with reduced clinical efficacy, infusion reactions, and hypersensitivity-like reactions.³⁰

However, safety data during an open-label extension of ENACT-2 revealed that one patient treated with natalizumab died of JC virus-associated PML. JC virus DNA was detected in frozen blood samples taken from the patient 3 months after initiating open-label natalizumab monotherapy.³⁴ In addition, Elan and Biogen Idec reported two cases of JC virus-associated PML in patients treated with natalizumab for multiple sclerosis. Natalizumab was removed from the market in 2005 by Biogen Idec due to these safety concerns. Blockade of the α_4 integrin inhibits CD4+ and CD8+ lymphocytes that home to the gut via $\alpha_4\beta_7$, as well as to the CNS via $\alpha_4\beta_1$. One theory is that impaired $\alpha_4\beta_1$ function may cause a deficiency in either CD4+ helper T cells or CD8+ cytotoxic T cells crossing the blood–brain barrier, thus disrupting the normal homeostatic control of JC virus infection. Natalizumab was returned to the market in 2006 for multiple sclerosis in association with a strict TOUCH patient and provider education and monitoring program for PML. Based on the results of the ENACT and ENCORE trials, natalizumab was approved by the FDA in 2008 for use as monotherapy only in the treatment of moderate to severely active CD. However, its approval required strict postmarketing surveillance and requires a CD-specific TOUCH program for education and monitoring for PML.

Vedolizumab (Entyvio or MLN0002)—Vedolizumab is a humanized mAb developed by Millennium Pharmaceuticals (Cambridge, MA) and approved by the FDA for the treatment of both moderate to severe UC and CD in May 2014, based on the results of two multicenter phase III clinical trials. Unlike natalizumab, vedolizumab targets the entire $\alpha_4\beta_7$ integrin, which in theory should eliminate any associated risk of PML since $\alpha_4\beta_7$ is specifically expressed on T cells that home to the intestine (**Figure 2**). In the GEMINI I trial, 374 patients with moderate to severely active UC were randomized to receive either 300 mg

vedolizumab infusion or placebo at days 1 and 15. Induction of a clinical response was assessed at 6 weeks. Patients who responded were enrolled in an open-label maintenance phase (along with responders from an additional cohort of 521 vedolizumab-treated patients) and randomized to receive either vedolizumab every 4 or 8 weeks or placebo for up to 52 weeks.³⁵ Induction results showed a 6-week clinical response rate of 47.1 in vedolizumab-treated patients, compared to 25.5% with placebo ($P < 0.001$). In addition, vedolizumab was effective at maintaining clinical remission through 52 weeks in 41.8% of patients receiving infusions every 8 weeks and 44.8% of patients treated every 4 weeks, compared to 15.9% of patients who were maintained on placebo. No differences in the occurrence of adverse events were observed between groups. A parallel phase III trial (GEMINI II) was performed in patients with moderate to severely active CD.³⁶ The two primary endpoints for the induction phase were defined as clinical remission (CDAI < 150) and clinical response (100-point decrease in CDAI) at week 6, and the primary endpoint for the maintenance phase was clinical remission at 52 weeks. During the induction phase, 14.5% of vedolizumab-treated patients achieved clinical remission by week 6, compared to 6.8% of patients who received placebo ($P = 0.02$); no difference was observed in clinical response rates (31.4% vs. 25.7%, $P = 0.23$). Among responders, 39.0% and 36.4% of patients who were maintained on vedolizumab every 8 and 4 weeks, respectively, were in remission at 52 weeks, compared to 21.6% of patients maintained on placebo ($P < 0.001$ and $P = 0.004$ vs. placebo, respectively). Patients treated with vedolizumab were more likely to experience nasopharyngitis, but less likely to have headache or abdominal pain. Of the 1,434, only 56 patients (4%) had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. In UC and CD trials, 4% of patients treated with vedolizumab and 3% of placebo patients experienced infusion-related reactions. In addition, one case of anaphylaxis was reported in a CD patient during infusion. These data were the basis for the recent FDA approval of vedolizumab in May 2014, and indicate that the drug is an effective therapy for UC, especially in patients who have failed anti-TNF therapy or to avoid surgical intervention. More studies are needed to identify the optimal niche for vedolizumab in medical management of CD. Another anti- $\alpha_4\beta_7$ mAb developed by Amgen (Thousand Oaks, CA; AMG 181) is currently in clinical trials for the treatment of both UC and CD.

Etrolizumab—Etrolizumab is a humanized anti- β_7 mAb currently under development by Hoffmann-La Roche (Nutley, NJ) for the treatment of UC. Etrolizumab blocks intestinal-specific lymphocyte recruitment via $\alpha_4\beta_7$ /MAdCAM-1, as well the interaction of $\alpha_E\beta_7$ and its natural ligand, E-cadherin, which is thought to mediate recruitment of $\alpha_E\beta_7^+$ intraepithelial lymphocytes. A recent phase II randomized, double-blind, placebo-controlled trial assessed the safety and efficacy of subcutaneous etrolizumab in moderate to severely active UC.³⁷ The study reported a 21% remission rate in patients treated with a 100-mg dose of etrolizumab, and a 10% rate in patients receiving a 300-mg dose, compared to a 0% remission rate with placebo ($P = 0.004$ and 0.048 vs. placebo, respectively). Adverse events were comparable between the groups. Based on these results, a phase III trial to assess the efficacy and safety of etrolizumab for induction and maintenance of remission in moderate to severely active UC patients who are refractory or intolerant to TNF inhibitors is currently underway and due to be completed in December 2018.

PF-00547659—PF-00547659 is an anti-MAdCAM-1 mAb currently under clinical development by Pfizer (Groton, CT).³⁸ An ongoing phase II placebo-controlled clinical trial (TURAN-DOT) is underway to study four doses of subcutaneous injection of PF-00547659 in patients with moderate to severely active UC. The study was initiated in November 2012, and data collection is expected to be completed by September 2014.

Targeting intestinal-specific chemokine/chemokine receptor complexes

The concept of inhibiting leukocyte trafficking to the inflamed intestine through the use of mAbs that inhibit integrin–adhesion molecule interactions has generated a modest second wave of therapeutic advancements for IBD, especially for patients with UC. An alternative approach to inhibiting lymphocyte recruitment is blockade of intestinal-specific chemokines/receptors complexes that act as a chemoattractants for circulating lymphocytes.

Vercirnon (Traficet-EN or CCX282-B)—CCR9 is a chemokine receptor that is expressed on the cell surface of memory/effector T cells and selectively binds to the potent small intestinal lymphocyte chemoattractant CCL25 (TECK). The interaction of CCL25/CCR9 promotes adherence and migration of T lymphocytes and IgA antibody secreting cells into the small intestinal lamina propria and epithelial compartments. Vercirnon is an orally active small molecule CCR9 antagonist that acts as a selective and potent inhibitor of CCL25-mediated lymphocyte chemotaxis.³⁹ The drug, developed by ChemoCentryx (Mountain View, CA) and GlaxoSmithKline (Philadelphia, PA), held considerable promise due to its small bowel specificity and its unique status as an orally administered therapy. Although a phase II double-blind, randomized, placebo-controlled trial (PROTECT-1) did not achieve its primary endpoint of clinical response at 8 weeks, the study was interpreted positively since a clinically significant treatment effect was observed by 12 weeks (61% response rate in vercirnon-treated patients vs. 47% with placebo, $P = 0.04$).⁴⁰ Drug development proceeded with four planned phase III multicenter randomized controlled trials. However, in August 2013 the manufacturers announced that the first of four phase III trials (SHIELD-1) also did not achieve its primary endpoint of clinical response at 12 weeks.⁴¹ In addition, there was a dose-dependent increase in the frequency of adverse events. No further clinical trials are currently underway at this time.

BMS-936557 (MDX-1100)—BMS-936557 is a humanized mAb under development by Bristol-Myers Squibb (Princeton, NJ) that targets interferon- γ -inducible protein (IP)-10 (CXCL10), an intestinal chemokine secreted by intestinal mucosal macrophages, lymphocytes, and endothelial cells that binds to the CXCR3 chemokine receptor on activated T lymphocytes. Microarray analysis showed that both molecules are overexpressed during active inflammation in the colonic lamina propria of patients with CD and UC.^{42,43} IP-10 is a potent chemoattractant for activated leukocytes, and it can also act indirectly to promote T helper (Th)1 and Th17 cellular responses within the inflamed mucosa. An 8-week phase II randomized, double-blind, placebo-controlled trial of BMS-936557 was conducted in 109 patients with active UC to assess its efficacy as induction therapy. The primary endpoint of clinical response rate at day 57 was not achieved (52.7% in BMS-936557-treated patients vs. 35.2% with placebo, $P = 0.083$).⁴⁴ A second phase II clinical trial is currently nearing completion for evaluation of efficacy and safety of

BMS-936557 as induction and maintenance therapy for patients with moderate to severe refractory CD.

RPC 1063—RPC 1063 is a specific sphingosine-1-phosphate (S1P)—1 agonist developed by Receptos (San Diego, CA) that binds S1P, trapping lymphocytes in lymph nodes and causing peripheral lymphopenia. Interestingly, after drug withdrawal lymphocytes recirculate, reversing the lymphopenia. RPC 1063 is currently under evaluation in patients with moderate to severely active ulcerative colitis. Results are expected in 2015.

CONCLUSION

Blocking leukocyte trafficking has provided a new approach to decrease inflammation in patients with IBD. One of the advantages of this approach is the ability to target treatments specifically to the intestinal mucosa. However, as more drugs are evaluated one disadvantage of blocking leukocyte extravasation to the gut appears to be decreased efficacy compared to TNF inhibitory drugs. This is particularly important for patients with CD and UC who present with more systemic involvement and extraintestinal manifestations. Future efforts will be directed at developing leukocyte trafficking therapies with increased efficacy and decreased side effects, and to more clearly determine the mechanism of action of leukocyte adhesion in the context of interactions with other intestinal mucosal cells.

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Figure 1.

Leukocyte adherence and migration through the intestinal endothelium is a multistep process. It includes initial capture, selectin-mediated rolling to slow the leukocyte, activation, firm adhesion to the intestinal endothelial layer and arrest, transendothelial migration, and finally extravasation into the inflamed intestinal mucosal tissues.

Figure 2.

Multiple drugs targeting leukocyte trafficking to the inflamed mucosa have been or are currently under development for the treatment of IBD. Most of these novel therapeutics are monoclonal antibodies that specifically target integrins or their cellular adhesion molecule ligands, which together mediate leukocyte adhesion to the intestinal endothelium and control infiltration.

Table 1

Integrin-ligand interactions involved in leukocyte homing to the intestine

Integrin		Endothelial ligand
α Subunit	β Subunit	
α_L	β_2	ICAM-1
α_4	β_1	VCAM-1
α_4	β_7	MAdCAM-1
α_E	β_7	E-cadherin