ADHESION MOLECULES AS A THERAPEUTIC TARGET IN IBD

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ABSTRACT

Recruitment of circulating leukocytes to areas of inflammation is a key process in the pathophysiology of inflammatory bowel diseases, including ulcerative colitis (UC). This is a finely regulated multistep process in which specialised adhesion and signalling molecules mediate a series of sequential steps. Following activation, integrins expressed on the surface of leukocytes become the key mediators of firm adhesion and emigration through interaction with immunoglobulin superfamily molecules expressed on the vascular endothelium. The anti α4 antibody natalizumab has shown efficacy in inducing and maintaining response and remission in patients with moderate and severe Crohn's disease. However, a major safety setback involving the onset of progressive multifocal leukoencephalopathy (PML) in 1/1000 treated cases led to limitations on its clinical use and application in UC. The more selective anti α4β7 antibody vedolizumab has proven efficacious for inducing clinical and endoscopic remission in UC. Selective expression of the α4β7 receptor MAdCAM-1, which occurs predominantly in the intestine, may avoid the risk of those central nervous system infectious complications associated with the nonselective blockade of all α4 integrins. Moreover, treatment with anti-MAdCAM-1 or anti-α7 antibody (etrolizumab) showed promising results for inducing remission in UC. In conclusion, the development of safe and effective drugs that target these molecular components of the inflammatory response may yield novel, improved therapies for inflammatory bowel disease (IBD) that address as yet unmet needs.

Keywords: Adhesion molecules, inflammatory bowel disease, ulcerative colitis, integrins, natalizumab, vedolizumab, etrolizumab, MAdCAM-1.

INTRODUCTION

The hallmark of ulcerative colitis (UC) lesions is infiltration of the intestine by mononuclear cells, predominantly lymphocytes. This cellular infiltration is the result of increased leukocyte recruitment and proliferation in the inflamed organ, together with a decrease in apoptosis. Adhesion molecules are cell surface-expressed glycoproteins that mediate cell-cell and cell-extracellular matrix interactions. Apart from playing a prominent role in leukocyte recruitment, they mediate important interactions with extracellular components that determine the survival and activation of immune cells. Adhesion molecules therefore represent promising therapeutic targets for human inflammatory diseases, including UC.[1]

Some of the current challenges now hindering the development of effective and safe anti-adhesion drugs for inflammatory bowel disease (IBD) therapy include identification of the most relevant, but selective, targets that predominantly affect recruitment to the inflamed intestine while preserving immune surveillance in other organs.

LEUKOCYTE-ENDOTHELIAL CELL INTERACTIONS

Leukocyte recruitment is initiated by their interaction with the blood vascular endothelium, primarily within specialised postcapillary venules. This interaction between circulating leukocytes and venular endothelium involves a multistep process in which specialised adhesion and

signalling molecules participate in mediating each of a series of sequential steps. In the first step, leukocytes marginalised from the central venular blood flow make contact with the endothelium and initiate rolling along the vascular lumen. This rolling delays the transit of leukocytes and allows 'sampling' of the local microenvironment for potential activating factors (chemokines) expressed on endothelial cells. Activation of leukocytes through this interaction with chemokines constitutes the second step of leukocyte recruitment. Chemokines bind to serpentine receptors and trigger rapid intracellular signalling in leukocytes, leading to functional activation of cell-surface adhesion molecules (integrins) through conformational changes that facilitate cell arrest on the vessel wall. This firm arrest is also favoured by cytokine-induced upregulation of binding receptors on endothelial cells. The final step, known as transendothelial leukocyte migration, is similarly orchestrated by chemotactic gradients stemming from the perivascular compartment (Figure 1).[2] Each stage of leukocyte recruitment - i.e. rolling, firm adhesion, and transendothelial migration - involves the participation of different families of adhesion molecules, including the selectins and their ligands, integrins, and the immunoglobulin superfamily.

INTEGRINS, THEIR RECEPTORS, AND THEIR INVOLVEMENT IN LEUKOCYTE RECRUITMENT

Integrins are heterodimeric proteins consisting of non-covalently associated α and β subunits. Leukocytes can express 13 different integrins from the existing repertoire.[3] Six different integrins contain the β_1 (CD29), β_2 (CD18), or β_7 subunits and serve as key mediators of leukocyte-endothelial cell adhesion. Their expression patterns and ligand partners vary among leukocyte populations (Table 1).

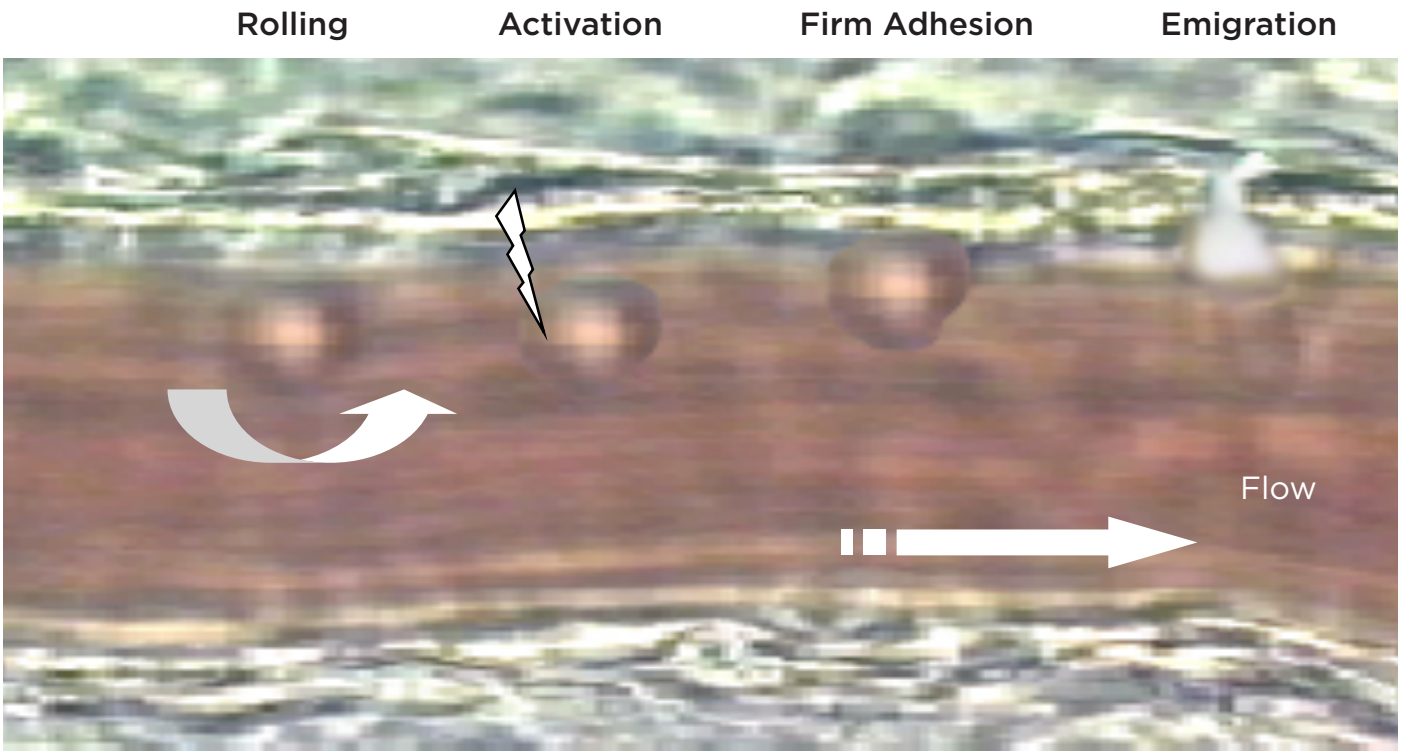

Figure 1. Steps of leukocyte recruitment.
Leukocyte-endothelial cell interactions. Schematic of the multistep model of leukocyte-endothelial cell adhesion. Fast moving leukocytes in the blood stream roll on activated endothelium via interactions between selectins and their ligands, or in some cases among integrin (α4)-immunoglobulin superfamily (MAdCAM-1) interactions. Selectins mediate the initial tethering and rolling interactions. Interactions between integrins and immunoglobulin superfamily members mediate firm adhesion and transmigration.

Table 1. Integrins and their receptors.

Adhesion Molecule	Location	Expression		Ligand	Function
		Constitutive	Inducible		
Integrin family					
CD11a/CD18 (LFA-1, $\alpha_L\beta_2$)	All leukocytes	Yes	No	ICAM-1, ICAM-2	Adhesion, emigration
CD11b/CD18 (Mac-1, $\alpha_M\beta_2$)	Granulocytes, monocytes	Yes	Yes	ICAM-1	Adhesion, emigration
CD11c/CD18 $\alpha_X\beta_2$	Granulocytes, monocytes	Yes	Yes	fibrinogen, C3b	Activation, adhesion?
$\alpha_4\beta_1$ (VLA-4)	Lymphocytes, monocytes, activated granulocytes	Yes	Yes	VCAM-1, fibronectin	Adhesion
$\alpha_4\beta_7$	Lymphocytes	Yes	No	MadCAM-1, VCAM-1, fibronectin	Rolling, adhesion
$\alpha_E\beta_7$	Lymphocytes, αE is also expressed by dendritic cell subsets	Yes	Yes	E-cadherin	Retention of cells in mucosal sites
Immunoglobulin superfamily					
ICAM-1 (CD54)	Endothelium, monocytes	Yes	Yes	CD11a/CD18, CD11b/CD18	Adhesion, emigration
ICAM-2	Endothelium	Yes	No	CD11a/CD18	Adhesion, emigration
VCAM-1 (CD106)	Endothelium	Yes	Yes	$\alpha_4\beta_1$, $\alpha_4\beta_7$	Adhesion, emigration
MadCAM-1	Endothelium (gut)	Yes	Yes	$\alpha_4\beta_7$, L-selectin	Adhesion, emigration
PECAM-1	Endothelium, leukocytes, platelets	Yes	No	PECAM-1, $\alpha_V\beta_3$?	Adhesion, emigration
VAP-1	Endothelium	Yes	Yes	?	Adhesion

$\alpha_L\beta_2$ (CD11a/CD18; LFA-1), which is primarily expressed by lymphocytes, interacts with intercellular adhesion molecule (ICAM)-1 and ICAM-2.[4] $\alpha_M\beta_2$ (CD11b/CD18) interacts with ICAM-1 on endothelial cells, and is also an important receptor for the complement fragment iC3b. Ligands for $\alpha_X\beta_2$ (CD11c/CD18) include fibrinogen and iC3b; binding of the latter results in cell activation.

A second subfamily of integrins combines the β_1 chain with different α subunits. The $\alpha_4\beta_1$ integrin (VLA-4) is involved in the adhesion of lymphocytes, monocytes, eosinophils, and natural killer cells with cytokine-activated endothelial cells. Ligands for VLA-4 include the vascular cell-adhesion molecule (VCAM)-1, as well as components of the extracellular matrix, such as fibronectin.

The $\alpha_4\beta_7$ heterodimer is highly expressed on a subset of lymphocytes that home towards the gut and gut-associated lymphoid tissues. This heterodimer recognises the mucosal endothelial ligand, mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), and mediates lymphocyte homing to Peyer's patches.[5] In addition to binding to MAdCAM-1, the $\alpha_4\beta_7$ integrin also binds to VCAM-1 and fibronectin.[6]

As mentioned above, some integrin receptors belong to the immunoglobulin superfamily of

adhesion molecules, which are characterised by the presence of multiple immunoglobulin-like domains. ICAM-1 is constitutively expressed on leukocytes, antigen-presenting cells, fibroblasts, epithelial cells, and endothelial cells. Moreover, it is upregulated upon activation by inflammatory mediators such as tumour necrosis factor alpha (TNF-α).[7,8]

VCAM-1 is an important mediator of lymphocyte and monocyte trafficking, through its interaction with the $\alpha_4\beta_1$ (VLA-4) as well as to $\alpha_4\beta_7$ integrins. Although VCAM-1 is absent on unstimulated human umbilical venule endothelial cells (HUVEC), transcription-dependent upregulation can be elicited by cytokines and lipopolysaccharides (LPS) in these cells.[7] In the murine intestine, the constitutive level of VCAM-1 expression is substantially lower than that of ICAM-1. However, profound increases in the endothelial cell-surface density of VCAM-1 are apparent within 5-9 hours of cytokine stimulation.[7]

The mucosal addressin MAdCAM-1 is mainly expressed on high endothelial venules of Peyer's patches and on venules of the small intestine and colon. MAdCAM-1 serves as a ligand for L-selectin and $\alpha_4\beta_7$ integrin, but not for $\alpha_4\beta_1$, which distinguishes it from VCAM-1. MAdCAM-1 participates in lymphocyte homing to Peyer's patches and in the recruitment of these cells into the intestine during inflammation.[2]

ADHESION MOLECULES IN HUMAN IBD

The contention that vascular endothelial cells are activated in the inflamed intestine of IBD patients is supported by the observation that the capacity of intestinal microvascular endothelial cells isolated from IBD patients to bind leukocytes increases dramatically, relative to those derived from control subjects.[9] It has also been shown that the culture supernatants of colonic mucosal biopsies from patients with UC or CD induce the upregulation of selectins and ICAM-1 in cultured human endothelial cells.[10]

Immunohistochemistry studies of intestinal mucosal biopsies from patients with IBD have demonstrated an increased expression of various endothelial adhesion molecules. In keeping with findings in animal models of IBD, an increased expression of P-selectin and E-selectin in venules and capillaries has been documented in inflamed areas from biopsies and surgically resected specimens in CD and UC.[11-14] Characterisation of ICAM-1 expression in human IBD has produced discrepant results, with initial studies reporting an increased expression of ICAM-1,[12,13] and later studies failing to confirm those findings.[11,14] It has also been observed that the proportion of venular endothelium within the lamina propria that expresses MAdCAM-1 is higher, compared with normal tissues, at inflammatory foci associated with UC and CD.[15] VCAM-1 expression in intestinal mucosa from IBD patients has been reported to be similar to that of controls,[11,12,14] a finding which contrasts with observations in experimental IBD demonstrating a consistent increase in VCAM-1 expression in diverse animal models. This is also at odds with studies involving soluble forms of adhesion molecules, which have shown a marked increase in soluble VCAM-1 in association with active IBD.

INTEGRINS AS TARGETS FOR THERAPEUTIC INTERVENTION

In contrast to members of the immunoglobulin superfamily of adhesion molecules, the function of integrins is regulated by conformational changes in affinity, rather than by changes in their expression levels. Independently of their mechanism of activation, adhesion molecule function can be blocked by means of neutralising monoclonal antibodies, which has proven to be a very effective strategy in limiting both acute and chronic forms of inflammation in animal models.[16-20]

In human IBD, three monoclonal antibodies targeting integrins (natalizumab, vedolizumab and etrolizumab) have been tested in different clinical trials, with the latter two now under development. Tables 2 and 3 summarise clinical trials using anti-adhesion molecule therapies conducted to date in CD and UC, respectively. Natalizumab is a recombinant IgG_4 humanised monoclonal antibody against the α4 integrin and was the first agent generated in the new selective adhesion-molecule inhibitor class. A humanised anti-$\alpha_4\beta_7$ integrin antibody, vedolizumab (MLN-0002), has also progressed to clinical trials in UC and CD. The latter has an IgG1 framework, although Fc-receptor recognition and binding is deleted and this antibody specifically inhibits α4β7 integrin binding with MAdCAM-1. Finally, the anti-β7 integrin antibody rhuMAb β7 has been tested in a Phase I study in UC (NCT00694980).[21]

Table 2. Clinical trials involving drugs targeting adhesion molecules in Crohn's disease.

Study; clinical phase	*Study design*	*Results*	*NCT number; status*
Gordon FH et al.[22] Phase I/II	30 pts with AD received 3 mg/kg infusion of Nat (n=18) or placebo (n=12). PE: CCR (defined as CDAI <150) at wk 2. Pts followed-up until wk 12. PK, tolerability, adverse events and QoL also assessed.	Mean plasma half-life of Nat: 4.8 days, most pts had detectable serum levels of Nat at 4 wks. 39% (7/18) of pts treated receiving Nat achieved complete CR at wk 2, compared to 8% with placebo. The most common adverse events, reported in at least 20% of patients during the 12-wk follow-up period did not significantly differ between the groups.	Completed
Ghosh S et al.[23] Phase II	A randomised, 12-wk study in 248 pts with moderate-to-severe disease in a double-blind, placebo-controlled trial. A four-arm study of Nat consisted of 2 infusions of placebo, 1 infusion of Nat (3 mg/kg) and 1 infusion of placebo, 2 infusions of Nat (3 mg/kg), and 2 infusions of Nat (6 mg/kg). PE: decrease of at least 70 points in CDAI at several time points until wk 12; and for SE: serum CRP and QoL evaluation.	Groups that received 2 infusions of Nat had higher remission rates than the placebo group at multiple time points. Rate of CR was significantly higher in all three Nat groups at wks 4, 6, and 8 than in the placebo group, with highest rate (71%) occurring at 6 wks in the group given 2 infusions of 3 mg/kg. The 2 infusions of 6 mg/kg of Nat and of 3 mg/kg had similar effect. All patients with Nat had a decrease in serum levels of CRP at wk 12, and an improvement in QoL at wk 6. By wk 12, only the groups that received 2 infusions of Nat maintained good QoL compared to the placebo.	Completed
Sandborn WJ et al.[24] ENACT-1 and ENACT-2 studies Phase II/III	Two controlled trials evaluated induction and maintenance therapy in pts with AD. Trial 1: 905 pts randomised to receive 300 mg of Nat or placebo at wks 0, 4, and 8. PE: decrease in CDAI score of at least 70 points, at wk 10. Trial 2: 339 pts randomised to receive 300 mg of Nat or placebo every 4 wks through wk 56. PE: sustained response through wk 36. A secondary outcome in both trials: disease remission (CDAI <150).	Nat and placebo groups had similar rates of response and remission at wk 10 in Trial 1. Higher rates of sustained response (61% vs. 28%) and remission (44% vs. 26%) through wk 36 were verified in the Trial 2. One patient died from progressive multifocal leukoencephalopathy, associated with the JC virus.	NCT00032786 and NCT00032799 Completed

CDAI: Crohn's disease activity index; PK: pharmacokinetics; QoL: Quality of life; CRP: C-reactive protein; wk: week; pts: patients; PE: primary endpoint; AD: active disease; CR: clinical response; Nat: natalizumab; Ved: vedolizumab; Ali: Alicaforsen.

Study; clinical phase	*Study design*	*Results*	*NCT number; status*
Targan SR et al.[25] ENCORE study Phase III	A 12-wk study designed to evaluate Nat efficacy of induction therapy in 509 pts with AD. PE: decrease of >70-point of CDAI at wk 8 sustained through wk 12.	48% of Nat-treated pts and 32% of placebo achieved response at wk 8, sustained through wk 12, with statistical significancy. The frequency and types of adverse events were similar between the groups.	Completed
Feagan BG et al.[36] Phase II	A randomised, double-blind, controlled trial including 185 pts randomised to receive Ved (MLN0002) 2.0 mg/kg, Ved 0.5 mg/kg, or placebo on days 1 and 29. PE: CR (decrease ≥70 points in the CDAI) on day 57. SE: clinical remission (CDAI score <150). PK, tolerability, adverse events and QoL were also assessed.	53% of pts who received Ved 2.0 mg/kg, 49% of those with Ved 0.5 mg/kg and 41% of placebo had CR at day 57. Clinical remission rates were 37%, 30%, and 21%, at day 57. There was 1 infusion-related hypersensitivity reaction.	Completed
Sandborn WJ et al.[37] GEMINI 2 study Phase III	A controlled trial to evaluate induction (wk 6) and maintenance therapy (wk 52) with Ved (300 mg) in pts with AD. 368 pts randomised to Ved or placebo at wks 0 and 2 (cohort 1), and 747 received open-label Ved at wks 0 and 2 (cohort 2). And for maintenance trial, 461 pts were randomised to receive placebo or Ved every 8 or 4 wks until wk 52. Clinical remission (CDAI ≤150) was assessed.	14.5% of the pts in cohort 1 who received Ved and 6.8% who received placebo achieved clinical remission. 39.0% of patients receiving Ved every 8 wks and 36.4% every 4 wks were in clinical remission at wk 52, compared with 21.6% receiving placebo. 24.4% of pts receiving Ved and 15.3% in the placebo group developed serious adverse events, the most common being infections.	NCT00783692 Completed
Yacyshyn B et al.[50] Phase I	331 pts with AD were included in a double-blind placebo-controlled trial to evaluate safety and efficacy (wk 12) of Ali intravenous therapy. PE: clinical remission at wk 12.	There was no difference in clinical remission of Ali-treated pts compared to placebo (33.9% versus 34.5%).	Completed

Table 3. Clinical trials involving drugs targeting adhesion molecules in ulcerative colitis.

Study; clinical phase	Study design	Results	NCT number; status
Gordon FH et al.[26] Phase I	A pilot study of 10 pts with AD, who received a single 3 mg/kg infusion of Nat. PE: decrease of Powell-Tuck score at 2 wks post-infusion. CRP, adverse events and QoL were also assessed.	5 pts achieved a CR at wk 2 and 1 more pt at wk 4, defined by Powell-Tuck score ≤5. 1 patient did not complete follow-up due to severe disease requiring urgent colectomy.	Completed
Feagan BG et al.[39] Phase II	A double-blind, placebo-controlled trial of Ved (MLN 02) therapy in AD designed to evaluate dose-response. 181 pts received Ved at 0.5 mg/kg or 2.0 mg/kg or placebo on day 1 and day 29. Clinical remission (a decreased of at least 3 points in the ulcerative colitis clinical score, a modification of the scoring system of the Mayo Clinic, MCS) and endoscopic remission (modified Baron score=0) was assessed at wk 6.	33% of pts who received Ved at 0.5 mg/kg, 32% of those with Ved at 2.0 mg/kg and 14% of placebo were in clinical remission at wk 6. 28% of pts who received Ved 0.5 mg/kg, 12% of those with Ved 2.0 mg/kg and 8% of placebo had endoscopic remission at wk 6.	Completed
Feagan BG et al.[38] GEMINI 1 study Phase II	A controlled trial to evaluate induction (wk 6) and maintenance therapy (wk 52) with Ved (300 mg) in pts with AD. 374 pts were randomised to receive Ved or placebo at wks 0 and 2 (cohort 1), and 521 received open-label Ved at wks 0 and 2 (cohort 2). For maintenance trial, 461 pts were randomised to receive placebo or Ved every 8 or 4 wks until wk 52. Clinical remission (decrease of 3 points in MCS and a decrease of at least 30% from baseline) was assessed.	47.1% of the pts in cohort 1 who received Ved and 25.5% who received placebo achieved clinical remission. 41.8% of pts receiving Ved every 8 wks and 44.8% every 4 wks were in clinical remission at wk 52, compared with 15.9% with placebo.	NCT00783718 Completed
Rutgeerts PJ et al.[21] Phase I	A double-blind, placebo-controlled trial of Etr therapy in moderate-to-severe disease designed to evaluate safety, PK and dose-response at day 29, 43, and 71. 49 pts participated on the study.	12/18 pts had clinical remission, compared with 4/5 placebo. 3/18 pts had clinical remission in the multiple dose stage, while 1/5 in placebo. Headache was the most common adverse event.	NCT00694980 Completed
Vermeire S et al.[45] Phase II	A double-blind, placebo-controlled study including 124 pts with AD that were randomised to Etr 100 mg monthly SC or 300 mg monthly SC + loading dose of 420 mg SC between wk 0 and 2 or placebo for 3 doses. PE: clinical remission at wk 10, defined as a total MCS of ≤2. SE: endoscopic remission (endoscopic score=0).	20.5% of pts treated with Etr 100 mg, 10.3% of those with 300 mg and 0% of placebo achieved clinical remission at week 10. In the anti-TNF-α naïve subgroup, the rates of clinical remission were significantly higher in the 100 mg dose group compared with placebo (43.8% versus 0%). 10.3% of pt treated with Etr 100 mg, 7.7% of those with 300 mg and 0% of placebo achieved endoscopic remission. In the anti-TNF-α naïve subgroup, endoscopic remission was 25% and 16.7% vs. 0% respectively.	Completed

DAI: disease activity index; MCS: Mayo Clinic Score; PK: pharmacokinetics; QoL: Quality of life; CRP: C-reactive protein; wk: week; pts: patients; PE: primary endpoint; AD: active disease; CR: clinical response; Nat: natalizumab; Ved: vedolizumab; Ali: Alicaforsen; Etr: etrolizumab; Mes: mesalazine.

Study; clinical phase	Study design	Results	NCT number; status
van Deventer SJ et al.[51] Phase I	40 pts with AD were included in a randomised, double-blind, placebo-controlled trial to evaluate safety and efficacy of Ali enema therapy. PE: assessment of DAI in several time points until month 6. Mean % change in DAI for each treatment group was evaluated at each time point and compared to placebo.	Ali at 2 and 4 mg/ml improved DAI by 72% and 68% compared with a placebo response of 11.5% at month 3. There were no significant differences between groups at month 6.	Completed
van Deventer SJ et al.[52] Phase II	A randomised, placebo-controlled, double-blind trial to evaluate efficacy and dose response (120 mg, 240 mg in 5 treatment arms) of Ali enema therapy in 112 pts with active distal disease and/or mild-to-moderate left-sided disease. PE: mean % change of DAI from wk 0 to 6. Mean % change in DAI for each treatment group was evaluated at each time point and compared to placebo.	No difference in DAI of Ali-treated pts compared to placebo (33.9% versus 34.5%). A reduction in mean % change of DAI relative to baseline was observed in the daily 240 mg Ali enema arm compared to placebo from wk 18 to 30.	Completed
Miner Jr PB et al.[53] Phase II	A randomised, double-blind, controlled trial with 159 pts with AD, to evaluate safety and efficacy of Ali enema (120 mg, 240 mg) compared to Mes enema (4 g). PE: DAI at wk 6 following either Ali enema or Mes enema therapy. DAI also assessed at different time points up to wk 54.	No significant difference in CR at wk 6 observed between treatment arms. Duration of response to Ali enema was 2 to 3-fold longer (128 and 146 days) compared to Mes (54 days).	Completed
Vermeire S et al.[54] Phase I/II	A randomised, double-blind, placebo-controlled study to evaluate safety and efficacy (remission based on Mayo score and on levels of faecal calproctectin) at wk 4 and 12. 80 pts with AD received single or multiple (3 doses, 4-wk intervals) doses of PF-00547,659 0.03-10 mg/kg IV/SC, or placebo. Endoscopic response assessed by ≥3-point reduction and 30% improvement in total Mayo score, and ≥1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1. Remission rates were defined as the proportion of patients with a total Mayo score ≤2 points with no individual subscore exceeding 1 point.	Rates of remission with PF-00547,659 were 13% at wk 4 and 22% at wk 12; and 11% at wk 4 and 0% at wk 12 for placebo group. Rates of endoscopic response were 42% in the PF-00547,659 group and 29% in the placebo group.	NCT00928681 Completed

Natalizumab

Several placebo-controlled studies involving hundreds of recruited patients have demonstrated the efficacy of natalizumab in achieving clinical remission in CD patients.[22-24] Nonetheless, Phase II and Phase III natalizumab trials failed to show statistically significant differences at the predefined endpoint. An additional Phase III induction study (ENCORE; Efficacy of Natalizumab in Crohn's Disease Response and Remission) involving 509 CD patients was conducted. This study achieved its primary efficacy endpoint: induction of response, defined as >70-point decrease from baseline in CDAI at week 8 sustained through week 12. Sustained remission occurred in 26% of natalizumab-treated patients and in 16% of patients receiving placebo ($p<0.002$).[25] The most promising results, however, were seen in the maintenance phase (ENACT-2).[24] 61% of CD patients receiving natalizumab maintained their response for an additional 6 months compared with 28% in the placebo group ($p<0.001$), and this significant difference was maintained for an additional 12 months.

This might be related to the drug's mechanism of action. If natailzumab exerts its beneficial effect predominantly by blocking leukocyte recruitment to sites of inflammation, once the inflammatory process is ongoing the infiltrating lymphocytes have a high resistance to apoptosis and may remain in the intestine, thereby perpetuating inflammation for considerable periods, and thus requiring administration of natalizumab for a prolonged period (10-12 weeks) in order to achieve a significant effect. On the other hand, once the inflammatory cells have been eliminated, prevention of further recruitment is very effective in countering a new relapse.

Data evaluating the efficacy of natalizumab treatment in UC are scarce. The only full publication available involves a pilot uncontrolled study, in which 10 patients with active UC, defined as a Powell-Tuck score >4, received a single infusion of natalizumab (3 mg/kg). The median Powell-Tuck score significantly decreased from 10.0 at baseline to 7.5 at week 2 and then to 6.0 at week 4. Five of the 10 patients achieved a clinical response, defined as a Powell-Tuck score of ≤5 by week 2, and one additional patient responded by week 4. Two patients achieved complete remission, defined as a score of 0. The median CRP at 2 weeks was also decreased.[26] Despite the positive efficacy demonstrated in this study, further investigation of natalizumab in UC is unlikely in the future due to life-threatening safety issues with the drug (see below) and the fact that surgery is a widely accepted option for UC patients refractory to current available therapies.

Safety of Natalizumab

The major setback in the clinical application of natalizumab has been reports of three serious infectious adverse events: onset of PML, which occurred in two patients (one fatal) treated in clinical trials for multiple sclerosis,[27,28] and one case (fatal) of a CD patient 3 months after initiation of open-label natalizumab treatment upon completion of participation in the ENACT-2 trial.[29] PML is a rare opportunistic infection of the central nervous system caused by the JC (John Cunningham, the first patient in whom the disease was recognised) virus.[30] PML is usually irreversible and fatal.

These three cases of PML in patients treated with natalizumab led the Food and Drug Administration (FDA) to withdraw the drug from the market in 2005. Following a safety evaluation, in >3,500 patients with multiple sclerosis (MS) or CD, that found no new cases of PML,[31] natalizumab was reintroduced to the market in 2006. Natalizumab is currently approved as a monotherapy for severe relapsing-remitting MS refractory to all other treatments, and for CD after failure of anti-TNF agents. Centres where natalizumab may be used are limited, and patients treated with the drug must participate in an extensive safety monitoring programme.[32] A recent report on this programme revealed that, of 37,600 patients being treated with this drug in the 3 years since the reintroduction of natalizumab to the market, there have been five additional cases of PML in patients with MS.[33] It is interesting to note that three recently reported cases of PML occurred in psoriasis patients treated with efalizumab, an antibody directed against the integrin αL (CD11a).[34]

Vedolizumab

Since natalizumab is an anti-α_4 antibody, it blocks both $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins, and consequently all VCAM-1 and MAdCAM-1 mediated leukocyte-endothelial cell interactions. It is conceivable that a more selective blockade may bring about

a more favourable safety profile; e.g. a blockade of $\alpha_4\beta_7$-MAdCAM-1 interactions, given the highly predominant expression of MAdCAM-1 in the gastrointestinal tract and the complete absence of expression of this molecule in the brain vasculature.[35] Vedolizumab (MLN-0002) is a blocking antibody against the $\alpha_4\beta_7$ integrin, and its efficacy for treatment of CD[36] and UC has been tested in Phase II studies, which have been followed by ongoing Phase III trials.[37,38]

The efficacy of vedolizumab for induction of remission in UC was assessed in a Phase II multicentre, double-blind, placebo-controlled trial in which 181 patients were assigned to receive vedolizumab (0.5 or 2.0 mg/kg) or placebo intravenously on days 1 and 29.[39] Clinical remission rates at week 6 were 33%, 32%, and 14%, respectively (p=0.03). The corresponding proportions of patients who improved by at least 3 points on the UC clinical score were 66%, 53%, and 33% (p=0.002). 28% of patients receiving 0.5 mg/kg and 12% of those receiving 2.0 mg/kg had endoscopically evident remission, compared with 8% of those receiving placebo (p=0.007). Human anti-human antibodies developed in 44% of those patients who received vedolizumab. High titres of anti-drug antibodies were present in 24% of patients and were associated with incomplete saturation of the $\alpha_4\beta_7$ receptor on circulating lymphocytes and no clinical benefits from treatment. No important differences in the occurrence of adverse events were identified among the treatment groups. No deaths, cancers, or opportunistic infections were observed.

The results of two integrated randomised, double-blind, placebo-controlled trials in UC have recently been published.[37,38] These studies evaluated the effect of vedolizumab (300 mg intravenously [i.v.]) at weeks 0 and 2 as induction (at week 6) and maintenance therapy (up to 52 weeks). A clinical response (decrease in the Mayo score of at least 3 points and no less than 30% from baseline with at least a 1-point reduction in the rectal bleeding subscore) was seen in 47.1% of vedolizumab-treated patients compared to 25.5% of placebo patients (p<0.001). At week 52, >40% of patients receiving vedolizumab every 4 or 8 weeks were in clinical remission (Mayo score ≤2 and no subscore >1), compared with 15.9% of patients who switched to placebo (p<0.001).

A significant benefit of vedolizumab was also reported for CD patients, although the results were less dramatic, and the frequency of adverse events higher than in UC.

rhuMAb β7 (Etrolizumab)

rhuMAb β_7 is a humanised IgG1 monoclonal antibody that targets the β_7 integrin subunit. Thus, while it may provide similar potential therapeutic benefits to vedolizumab by blocking $\alpha_4\beta_7$-dependent leukocyte recruitment and cell activation, it also recognises another β_7 integrin, $\alpha_E\beta_7$, which plays other roles in gut-associated immune responses. $\alpha_E\beta_7$ is expressed by most intra-epithelial lymphocytes (IELs) and binds to the epithelial E-cadherin expressed by the epithelium. It can also be expressed by some lamina propria lymphocytes (LPLs) with regulatory properties,[40] as well as a subset of tolerogenic dendritic cells resident in the intestine or associated lymphoid tissues.[41,42] Nonetheless, the functional role of α_E expression in these cell populations is not clear and, at least in α_E-deficient mice, expression of $\alpha_E\beta_7$ T cells is not needed to drive their accumulation in the intestine,[43] nor is it necessary for mesenteric lymph node dendritic cells to induce gut-tropic ($\alpha_4\beta_7$ and CCR9) receptors on T cells.[44]

A recently published randomised Phase I study evaluated the safety and pharmacology of rhuMAb β_7 in UC.[21] This study showed that while rhuMAb β_7 is safe in UC patients, it offers no significant benefits compared to the placebo, at least not in this small series of patients. Nonetheless, results from a Phase II study in UC patients show much more promise with etrolizumab (100 mg or 300 mg), demonstrating significantly higher rates of clinical remission compared to placebo at week 10, as well as increased endoscopic remission. The differences compared to placebo were even more pronounced in patients naïve to anti-TNF-α.[45]

IMMUNOGLOBULIN SUPERFAMILY ADHESION MOLECULES AS TARGETS FOR THERAPEUTIC INTERVENTION IN UC

Anti-ICAM-1

An antisense phosphorothioate oligodeoxynucleotide (ODN) to mouse ICAM

1, ISIS 3082, has been shown to be active in multiple models of inflammation, including dextran sulphate-induced colitis.[46] The human analogue alicaforsen (ISIS 2302)[47] has been tested in a pilot study in CD where it showed some benefits.[48] However, a blinded controlled study involving fixed doses of subcutaneous ISIS 2302 did not show higher effectiveness than the placebo.[49] The global results of two blinded controlled studies including a total of 331 patients with active CD also showed that the remission rates in the ISIS 2302-treated and placebo groups were similar.[50]

An enema formulation of ISIS-2302 for treatment of UC was tested in a small, randomised, placebo-controlled, double-blind, dose-escalating trial with encouraging results.[51] However, this study was followed by two larger and negative studies.[52,53] Further development of this drug in IBD is highly unlikely.

Anti-MAdCAM-1

Blocking MAdCAM-1 is a rational mechanism of action for therapeutic intervention in IBD, since its expression is mainly restricted to the gastrointestinal tract mucosa.[54] This organ specificity may translate to a favourable safety profile.

A recent Phase I study tested the safety and efficacy of a fully human anti-MAdCAM-1 IgG2 antibody (PF-00547,659) in patients with active UC.[54] In this double-blind, placebo-controlled study, 80 patients with active UC received a single dose or three doses at 4-week intervals of PF-00547,659 (0.03–10 mg/kg IV/SC) or placebo. No obvious side-effects were observed in the monoclonal antibody-treated patients, compared to placebo; importantly, there was no evidence of opportunistic infections. The active treatment arm had numerically higher response rates and remission rates at weeks 4 and 12, although none of these comparisons reached statistical significance.

Overall responder/remission rates at weeks 4 and 12 were 52%/13% and 42%/22%, respectively, for PF-00547,659 and 32%/11% and 21%/0%, respectively, for placebo. Faecal calprotectin levels decreased to a greater extent with PF-00547,659 than placebo (week 4: 63% versus 18%). In this study, no antidrug antibodies were detected during treatment up to week 12 for all patients, and no injection site reactions were observed. Longer-term studies involving a much larger number of patients are required and are now underway.

CONCLUSIONS

Several key steps in the inflammatory cascade that result in leukocyte recruitment appear amenable to pharmacological inhibition and represent an attractive target for the treatment of IBD, including UC. Although preliminary use in clinical practice has been encouraging, the challenges posed by the potential for disruption of alternate physiological processes, as well as immune suppression, remain significant. Given its intestinal mucosal restricted expression, modulation of the $\alpha_4\beta_7$-MAdCAM-1 interaction seems at present the more promising approach. The development of safe and effective drugs that target these molecular components of the inflammatory response may yield novel and improved therapies for UC patients.

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