Review article: nonclinical and clinical pharmacology, pharmacokinetics and pharmacodynamics of etrolizumab, an anti-β7 integrin therapy for inflammatory bowel disease

M. T. Tang | M. E. Keir | R. Erickson | E. G. Stefanich | F. K. Fuh | T. Ramirez-Montagut | J. M. McBride | D. M. Danilenko

Research and Early Development,
Genentech, Inc., South San Francisco, CA, USA

Correspondence
Dr. MT Tang, Clinical Pharmacology,
Genentech, Inc., South San Francisco, CA, USA.
Email: tang.meina@gene.com

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Summary

Background: Novel treatments with superior benefit-risk profiles are needed to improve the long-term prognosis of patients with inflammatory bowel disease (IBD). Etrolizumab—a monoclonal antibody that specifically targets β7 integrins—is currently under phase III clinical evaluation in IBD.

Aim: This review summarises the available pharmacological and pharmacokinetic/pharmacodynamic data for etrolizumab to provide a comprehensive understanding of its mechanism of action (MOA) and pharmacological effects.

Methods: Published and internal unpublished data from nonclinical and clinical studies with etrolizumab are reviewed.

Results: Etrolizumab exerts its effect via a unique dual MOA that inhibits both leukocyte trafficking to the intestinal mucosa and retention within the intestinal epithelial layer. The gut-selectivity of etrolizumab results from its specific targeting of the β7 subunit of α4β7 and αEβ7 integrins. Etrolizumab does not bind to α4β1 integrin, which mediates lymphocyte trafficking to tissues including the central nervous system, a characteristic underlying its favourable safety with regard to progressive multifocal leukoencephalopathy. Phase I/II studies in patients with ulcerative colitis (UC) showed linear pharmacokinetics when etrolizumab was administered subcutaneously at 100 mg or higher once every 4 weeks. This dose was sufficient to enable full β7 receptor occupancy in both blood and intestinal tissues of patients with moderate to severe UC. The phase II study results also suggested that patients with elevated intestinal expression of αE integrin may have an increased likelihood of clinical remission in response to etrolizumab treatment.

Conclusion: Etrolizumab is a gut-selective, anti-β7 integrin monoclonal antibody that may have therapeutic potential for the treatment of IBD.
1 | INTRODUCTION

The current goals of novel therapeutics for the treatment of Crohn’s disease and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are to induce and maintain steroid-free remission and achieve long-term mucosal healing, so as to reduce/eliminate the need for IBD-related hospitalisation and surgery, improve patient quality of life and avoid disability.1-3 The current standard of care includes 5-aminosalicylates (5-ASAs), which are used as first-line therapy for UC. However, ~50% of patients do not respond to 5-ASAs alone and require more aggressive intervention with corticosteroids and/or immunosuppressant therapy (eg azathioprine, mercaptopurine and methotrexate). Corticosteroid and immunosuppressant therapies, however, are often associated with significant side effects or intolerance and may have limited efficacy; for example, corticosteroids have not shown benefit in the maintenance settings.4,5 In patients who do not achieve or maintain remission in response to corticosteroids or immunosuppressants, biologic therapy options including monoclonal antibodies (mAbs) targeting tumour necrosis factor α (TNF-α), such as infliximab (Remicade, Janssen Biotech Inc., Horsham, PA, USA) and adalimumab (Humira, AbbVie, Chicago, IL, USA), can be used to induce and maintain remission.6,7 Overall, the benefit-risk profiles for anti-TNF-α biologics are considered acceptable. However, approximately 10%-30% of IBD patients are primary nonresponders to anti-TNF-α therapy, and another approximately 20%-40% of IBD patients stop responding to anti-TNF-α therapy over time.8,9 In addition, these TNF-α inhibitors are associated with increased risk of infections and IBD-related complications stemming from inadequate disease control.10-12 In addition to offering better benefit-risk profiles, new innovative and effective therapies will also positively influence the balance of cost-effectiveness by lowering healthcare utilisation, given that IBD was the primary cause for 1.36 and 1.9 million physician visits per year in the United States in 2004 and 2009, respectively, and the first-listed discharge diagnosis in over 100 000 hospitalisations.13 Hence, there continues to be a need for novel treatments with improved benefit-risk profiles that enhance the long-term prognosis of patients with IBD.

Binding of integrins to their ligands controls leucocyte trafficking and retention within peripheral tissues, such as the gut, and modulates the local inflammatory milieu; thus, integrins are emerging therapeutic targets for the treatment of IBD. Natalizumab (anti-α4 integrin; Tyasbri, Biogen, Cambridge, MA, USA) is approved for Crohn’s disease in the United States,14 whereas vedolizumab (an anti-integrin mAb targeting α4β7 heterodimers; Entyvio, Takeda, Osaka, Japan) is on the market for the treatment of both UC and Crohn’s disease.15,16 Etrolizumab (also called rhuMAb β7; Genentech, San Francisco, CA, USA), currently under evaluation in clinical studies for its therapeutic potential in IBD, is an IgG1-humanised monoclonal antibody that specifically targets the β7 subunit of both the α4β7 and αEβ7 integrins. Binding to β7 integrin enables etrolizumab to block both leucocyte trafficking to the gut via α4β7 interactions with its endothelial ligand mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1),17,18 expressed primarily on endothelium of venules of intestinal lamina propria and associated lymphoid tissues,19,20 as well as the retention of lymphocyte subsets within the intestinal mucosa through the interaction of αEβ7 with its ligand E-cadherin, expressed on the gut epithelium21 (Figure 1, Table 1).22-25

The objectives of this review are to summarise the available published and unpublished nonclinical and clinical pharmacological, pharmacokinetic (PK) and pharmacodynamic (PD) data for etrolizumab, and to provide a comprehensive understanding of its mechanism of action (MOA) and pharmacological effects. Since etrolizumab has a unique dual MOA associated with inhibition of both the α4β7 and αEβ7 pathways, the integrated pharmacological information summarised in this review aims to provide researchers and investigators with a clear view of its unique biology distinct from other anti-integrin drugs in the class.

1.1 The role of β7 integrins and their ligands

Integrins are cell surface glycoprotein receptors that play a role in a wide range of cell-cell and cell-matrix interactions during embryogenesis, thrombosis and leucocyte adhesion, signalling, proliferation and migration.26 They are composed of heterodimeric, noncovalently interacting α and β subunits that bind distinct cell adhesion molecules (CAMs) on endothelia, epithelia and the extracellular matrix. This review focuses on leucocyte homing mediated by integrin binding to tissue-specific CAMs to regulate cell recruitment from the peripheral circulation into tissues.27

α4β7 integrin plays a crucial role in leucocyte homing to the intestinal mucosa and associated lymphoid tissues. α4β7 integrin is constitutively expressed at a modest level on naive T and B cells and at higher levels on intestinal-homing effector/memory T and B cells. In contrast, effector/memory T and B cells that are activated to home to nonintestinal tissue express low levels of α4β7 integrin. Additionally, α4β7 integrin is also expressed on NK cells, stimulated monocytes, macrophages, mast cells, eosinophils and basophils.28,29 In the gut, firm adhesion of leucocytes to the mucosal endothelium is initiated by chemokine signals which induce a conformational change in the α4β7 heterodimer on leucocytes that enable binding to MAdCAM-1 with high affinity. This engagement slows leucocyte movement along the endothelial surface, eventually arresting the cell before extravasation through the vascular endothelium to underlying tissue.27 T lymphocytes bearing α4β7 preferentially bind to endothelial venules expressing MAdCAM-1 in intestinal tissue as well as to the extracellular matrix molecule fibronectin fragment CS-1.30-32 The endothelial cell surface protein vascular cell adhesion molecule-1 (VCAM-1) also interacts with α4β7, albeit with a slightly lower affinity compared with its interaction to MAdCAM-1.33 These relative binding affinities are not necessarily static, as distinct chemokine-induced β7 phosphorylation states exist that promote α4β7 cell adhesion via MAdCAM-1 while suppressing binding to VCAM-1 and vice versa.34 Both the extent of α4β7 cellular infiltrates and MAdCAM-1 expression are increased in the intestinal tracts of patients with UC or Crohn’s disease.19,34 The
The majority of β7 integrin-expressing cells in the circulating lymphocytes (including T and B cells) are α4β7+ cells.24 αEβ7 integrin is found primarily on intraepithelial lymphocytes (IEL) and lamina propria T lymphocytes within mucosal tissues. Indeed, mucosal T lymphocytes expressing αE (also known as CD103) are significantly enriched in intestinal tissue compared with lung and the spleen.25 The finding that more than 90% of IELs and 50% of T lymphocytes in the human intestinal lamina propria express α4β7 and αEβ7 integrins suggests a critical role for these molecules in lymphocyte homing and retention in mucosal tissues. The summary of monoclonal antibodies targeting integrins and currently approved or under development for the treatment of IBD is presented in Table 1.}

### Table 1: Summary of monoclonal antibodies targeting integrins and currently approved or under development for the treatment of IBD

| Anti-integrin | Antigen target | Targeted integrins | Integrin ligands | Molecule type | Indication | Reference |
|---------------|----------------|--------------------|------------------|---------------|------------|-----------|
| Natalizumab (Tysabri) | α4 | α4β1, α4β7 | VCAM-1, MAdCAM-1 | Humanised mAb, IgG4 | Crohn’s disease | Byron et al.22; Newham et al.23 |
| Vedolizumab (Entyvio) | α4β7 | α4β7 | MAdCAM-1 | Humanised mAb, IgG1 | Crohn’s disease | Wyant et al.25 |
| Etrolizumab | β7 | α4β7, αEβ7 | MAdCAM-1, E-Cadherin | Humanised mAb, IgG1 | Crohn’s disease | Vermeire et al.24 |

Ig, immunoglobulin; mAb, monoclonal antibody; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; MS, multiple sclerosis; UC, ulcerative colitis; VCAM, vascular cell adhesion molecule.
αE supports a distinct role for this integrin in mucosal immunology. αE expression has also been described on dendritic cells, mast cells, and innate lymphoid cells (ILCs). The αE integrin is only known to dimerize with the β7 integrin, a process critical for the translocation of αEβ7 to the cell surface to enable cell binding to E-cadherin. β7 integrin on leucocytes binds specifically to E-cadherin on epithelial cells and is thought to mediate the retention of cells, particularly IELs, in mucosal tissue. Anti-αEβ7 antibody treatment has been shown to attenuate the severity of colitis in a mouse experimental colitis model, suggesting a pathogenic role for αEβ7+ lymphocytes in experimental models of IBD.

Recent data show that there are notable differences between αE+ and αE− T cells from healthy control and UC colonic biopsies, with an overall increased proportion of CD3+ αE+ T cells and a 2-fold increase in CD4+ αE+ T cells in active UC disease. Furthermore, an association of αEβ7 integrin expression with pro-inflammatory CD4+ T cells including Th1, Th17 and Th17/Th1 cells in the colons of UC patients reinforces the potential importance of these cells in disease pathogenesis. In addition to their integral role in GI tract homeostasis as well as in IBD, β7 integrins and their ligands have also been implicated as playing a role in several inflammatory pathologies. The strongest evidence for a pathologic role for β7 integrins is in hepatic inflammatory conditions, including primary sclerosing cholangitis, where the ligand of α4β7 integrin, MAdCAM-1, is upregulated. Previous studies also show increased β7 integrin-expressing T cells and in particular αE-expressing cells in coeliac disease, psoriasis and spondyloarthopathies; however, the evidence in these conditions is less compelling and needs further investigation.

1.2 | Role of α4β7 and αEβ7 integrins in the pathobiology of IBD

The pathobiology of IBD is driven primarily by pro-inflammatory pathways which damage mucosal tissue and inhibit healing. In healthy controls, αE memory CD4+ T-helper lymphocytes secrete interferon (IFN)-γ, TNF-α and interleukin (IL)-17A. Recent experimental evidence suggests that in patients with IBD, αE memory CD4+ T helper lymphocytes produce more of the pro-inflammatory cytokines IFN-γ, TNF-α and IL-17A compared with non-IBD controls. Likewise, T-helper 9 (Th9) lymphocytes, which produce IL-9, a cytokine that inhibits epithelial repair, express high levels of αE relative to other T-helper lymphocytes and are also increased in patients with UC. In addition, cytoplasmic granules, including granzyme A, secreted by CD8+ αE and CD4+ αE T lymphocytes have been shown to be more prevalent in the gut tissue of patients with IBD compared with non-IBD controls. In patients with Crohn’s disease, αE+ intraepithelial type 1 ILCs have also been found to be elevated. Experiments in a murine anti-CD40-induced colitis model suggest that αE+ intraepithelial type 1 ILCs contribute to the inflammatory process. Consistent with this finding, anti-αE treatment reduced the severity of colitis in a murine model of experimental colitis. Moreover, a recent study evaluating the trafficking of lymphocytes derived from UC patients to inflamed murine gut in a humanised mouse model supports the notion that targeting both α4β7 and αEβ7 may be more efficacious than targeting α4β7 exclusively. Zundler et al demonstrated that the dual blockade of αEβ7 and αEβ7 integrins reduced immune cell infiltration in the colon compared with blockade of anti-α4β7 alone. Collectively, these data support an important role for αE+ T cells in IBD pathophysiology.

2 | ETROLIZUMAB: PHARMACOLOGY AND MOA

2.1 | In vitro data

2.1.1 | Binding affinity and specificity

Etrolizumab is a humanised mAb derived from the rat anti-mouse/human β7 mAb FIB504. The humanised version of FIB504 antibody, huFIB504, was generated by grafting heavy and light chain complementarity-determining regions cloned from the rat FIB504 hybridoma line onto a backbone that consisted of human immunoglobulin (Ig) G1 subgroup-III Vh, κ subgroup-1 Vκ consensus sequences. The huFIB504 antibody was further engineered to generate the final etrolizumab mAb used in the clinical studies. This full-length, recombinant antibody consists of 2 heavy chains (446 residues) and 2 light chains (214 residues). Etrolizumab binds the β7 subunit of both α4β7 and αEβ7 integrins with high affinity, although the binding affinity of etrolizumab for human α4β7 (as determined by equilibrium binding analysis to HEK293 cells transfected with the appropriate integrin) was a log-fold stronger (Ka = 116 ± 11 pmol l−1) (Mean ± SD) compared with its affinity for human αEβ7 (Ka = 1800 ± 170 pmol l−1). Etrolizumab binds the β7 integrin subunit on lymphocytes from mice, rabbits and cynomolgus monkeys with high affinity (Table 2), allowing for translation of pharmacological findings across these different nonclinical species.

Cell attachment assays were used to evaluate the in vitro potency of etrolizumab. In α4β7-expressing cells, etrolizumab blocked the interaction of α4β7 with its cognate ligands MAdCAM-1 and VCAM-1, with 50% inhibitory concentration (IC50) of 0.075 ± 0.034 nmol l−1 (Mean ± SD) and 0.089 ± 0.009 nmol l−1, respectively. In similar cell adhesion experiments, etrolizumab blocked the interaction between αEβ7 and its ligand E-cadherin with an IC50 of 3.96 ± 1.78 nmol l−1 (Table 3). These data indicate that etrolizumab is potent in inhibiting in vitro adhesion of α4β7+ bearing cells to human MAdCAM-1 or VCAM-1.

In addition, etrolizumab is highly specific for the β7 subunit of α4β7 and αEβ7 and does not bind to α4 or β1 integrin subunits. Experiments with α4β1+/α4β7 Ramos cell line binding to human VCAM-1 showed that etrolizumab did not inhibit α4β1+ cell adhesion at concentrations as high as 100 nmol l−1 (Figure 2), indicating that the migration of T-lymphocyte subsets expressing α4β1 but not α4β7 should not be affected by etrolizumab.
TABLE 2  Etrolizumab affinity data for binding to α4β7 or αEβ7 transfected human HEK293 cells or mouse 38C13 cells, or human peripheral blood lymphocytes

| Blairex Fab $K_d$ (nmol l$^{-1}$) | Equilibrium binding analysis (pmol l$^{-1}$) |
|---------------------------------|----------------------------------|
| Human α4β7                     | Human α4β7-293$^{67}$ | Human αEβ7-293$^{67}$ | Human PBLs | Cyno PBLs | Rabbit PBLs | Mouse α4β7-38C13 |
| Etrolizumab                    | 18                  | 116 $\pm$ 11$^b$           | 1800 $\pm$ 170$^c$ | 31.7 $\pm$ 8.1$^d$ | 25.7 $\pm$ 4.0$^d$ | 57$^d$ | 181$^d$ |

Cyn, cynomolgous monkey; PBL, peripheral blood lymphocytes.

$^a$n = 4.

$^b$n = 3.

$^c$n = 2.

TABLE 3  Etrolizumab and anti-α4 (natalizumab) inhibition of β7$^+$ cell binding to ligands in cell attachment assays

| Cells Ligand                   | IC$^{50}$ (nmol l$^{-1}$) | Control (6B11) | Natalizumab | Etrolizumab |
|--------------------------------|-------------------------|---------------|-------------|-------------|
| RPMI 8866 MAdCAM-1-Ig          | >100                    | 0.35 $\pm$ 0.04 | 0.075 $\pm$ 0.034 |
| RPMI 8866 VCAM-1-Ig            | >100                    | 0.196$^a$     | 0.089 $\pm$ 0.009 |
| RPMI 8866 Fibronectin (FN40)    | >100                    | 0.32$^a$      | 0.119 $\pm$ 0.056 |
| αEβ7-293 E-Cadherin            | >100                    | >100          | 3.96 $\pm$ 1.78 |

IC$^{50}$, 50% inhibitory concentration; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; VCAM-1, vascular cell adhesion molecule. RPMI8866 is a human B-cell line; 6B11 is a nonblocking anti-β7 negative control antibody.

$^a$n = 1. For all other measurements, n = 3.

2.2 | In vivo data

2.2.1 | Nonclinical in vivo pharmacological data

Several in vivo experimental animal models demonstrate that etrolizumab specifically blocks intestinal homing but does not interfere with leucocyte homing to other tissues. In the CD45RB$^+$ CD4$^+$ T cell-reconstituted severe combined immunodeficiency mouse model of IBD, etrolizumab blocked homing of radiolabelled lymphocytes to the inflamed colon but had no effect on lymphocyte homing to the spleen.$^{56}$ This supports the hypothesis that etrolizumab specifically blocks lymphocyte homing to the inflamed GI tract and has no apparent effect on lymphocyte trafficking to peripheral lymphoid tissues.

In addition, studies in cynomolgus monkeys demonstrated that animals dosed with etrolizumab increased their peripheral blood β7$^{High}$ CD45RA$^-$ “gut homing memory” CD4$^+$ T lymphocytes but had no substantial effect on β7$^{Low}$ CD45RA$^-$ “peripheral homing memory” CD4$^+$ T lymphocytes or β7$^{Intermediate}$ CD45RA$^-$ naive CD4$^+$ T-helper lymphocytes.$^{55}$ The increase in peripheral β7$^{High}$ lymphocytes, presumably due to the inhibition of the trafficking mechanisms of these cells to gut tissue, correlated with the complete peripheral cell β7 receptor occupancy (RO) by etrolizumab. Subsequent wash-out of etrolizumab from the circulation led to the loss of complete β7 RO and the recovery of peripheral β7$^{High}$ lymphocytes towards baseline levels.$^{56}$

Furthermore, in etrolizumab-dosed cynomolgus monkeys and mice, dose-dependent and reversible decrease in lymphocytes in the GI-associated lymphoid tissue (GALT) in cynomolgus monkeys and the intestinal lamina propria in mouse were observed by semi-quantitative histological evaluation.$^{57}$ No changes in lymphocyte numbers were observed in any non-gut tissues, including the central nervous system (CNS). Importantly, despite the decrease in intestinal lymphocytes, there was no evidence of GI tract infections or any other adverse finding in either species, indicating that the observed pharmacological effect of etrolizumab on the GI tract was without any associated toxicological effects.

Treatment with the anti-α4β1 integrin antibody natalizumab has been associated with an increased risk of progressive multifocal...
leuencephalopathy (PML), an opportunistic brain infection caused by the John Cunningham virus. Thus, leucocyte homing to the CNS has been deemed an important safety consideration.\textsuperscript{58} Accordingly, a myelin basic protein/T-cell receptor (MBP-TCR) transgenic mouse model of experimental autoimmune encephalomyelitis (EAE) was used to assess the potential effect of the murine anti-\(\beta 7\) mAb muFIBS04 on lymphocyte homing to the CNS. While muFIBS04 had no effect on EAE disease severity as assessed by leucocytic infiltration into the CNS or improvement of survival, the murine anti-\(\alpha 4\) antibody (mPS/2) significantly decreased leucocytic infiltration into the CNS and reduced EAE disease severity and death.\textsuperscript{56,57} These data clearly demonstrate that the \(\alpha 4\beta 7\) integrin is not involved in inflammatory cell recruitment across the blood-brain barrier, while the \(\alpha 4\beta 1\) integrin is.\textsuperscript{57,59} In addition, in other models of chronic CNS inflammation, CD\textsuperscript{4} memory T-lymphocyte infiltrates in the CNS do not express \(\alpha 4\beta 7\), \(\alpha 6\) or \(\alpha E\) integrin but instead, strongly express \(\alpha 4\beta 1\).\textsuperscript{59,60} Furthermore, MAdCAM-1 (the ligand for \(\alpha 4\beta 7\)) is not expressed on cerebral endothelial vessels, perivascular tissue, the meninges and grey and white matter in healthy controls and patients with multiple sclerosis.\textsuperscript{61-64} Thus, the absence of expression of both \(\alpha 4\beta 7\) and MAdCAM-1 in CNS tissue suggests that etrolizumab should not interfere with lymphocyte trafficking to the brain.

These in vivo mechanistic studies and the comparison of anti-\(\beta 7\) and anti-\(\alpha 4\) in EAE models convincingly demonstrate that etrolizumab and anti-\(\alpha 4\) integrin antibodies have distinct effects on leucocyte homing, namely that etrolizumab specifically targets intestinal homing of leucocytes but does not affect systemic homing, including trafficking to the CNS. These data suggest that the risk for inducing PML with etrolizumab is significantly lower than with those anti-integrins that target \(\alpha 4\) integrin.

3 | CLINICAL STUDIES

3.1 | Overview of etrolizumab clinical studies

Following the successful completion of phase I and II studies and an additional phase II open-label extension study (OLE), etrolizumab is currently being evaluated in multiple ongoing phase III clinical studies (ClinicalTrials.gov: NCT02394028, NCT02165215, NCT02136069, NCT02100696, NCT02163759, NCT02171429, NCT02118584, NCT02403323).

In a phase I study assessing safety and tolerability (ClinicalTrials.gov: NCT00694980), patients with moderately to severely active UC received etrolizumab either intravenously (IV) or subcutaneously (SC) as a single dose (0.3-10 mg/kg) or as multiple doses (0.5-4 mg/kg) administered every 4 weeks (q4w) for a total of 3 doses.\textsuperscript{65} A subsequent phase II multicentre study (EUCALYPTUS, ClinicalTrials.gov: NCT01336465) enrolled patients with moderate to severe UC into 3 SC dose arms (1:1:1): etrolizumab 100 mg (nominal) administered q4w; etrolizumab 420 mg at week 0 (loading dose [LD]) followed by 300 mg (nominal) at weeks 2, 4 and 8, or matching placebo injections given at weeks 0, 2, 4 and 8. Clinical activity of etrolizumab was demonstrated in EUCALYPTUS as measured by the induction of clinical remission defined as Mayo clinic score (MCS) \(\leq 2\) and no individual subscore >1. The overall proportion of patients in clinical remission with etrolizumab was 21% in the 100 mg cohort (\(n = 39\)) and 10% in the 300 mg + LD cohort (\(n = 39\)), compared with 0% in the placebo cohort (\(n = 41\)); but the majority of patients achieving clinical remission (83%) were from the TNF-naive population. Among TNF-naive patients, 44% in the 100 mg cohort (\(n = 16\)) and 25% in the 300 mg + LD cohort (\(n = 12\)) were in clinical remission at 10 weeks compared with 0% of patients in the placebo cohort (\(n = 15\)).\textsuperscript{24} UC patients in EUCALYPTUS were allowed to cross over into an OLE study (SPRUCE, ClinicalTrials.gov: NCT01461317) in which 108 patients were treated with etrolizumab for a median of 6.9 months (range: 0.8-54.3 months).

Overall rates of adverse events (AEs) in the etrolizumab-treated patients of the EUCALYPTUS study were similar to those in the placebo arm.\textsuperscript{24} Notably, rates of infections were similar among all groups. Mild injection site reactions (ISRs) were reported in the 300 mg + LD cohort, but no severe hypersensitivity reactions were seen.

3.2 | Clinical pharmacology

3.2.1 | Clinical PK and population PK analyses

PK data from etrolizumab-treated patients, which included those collected during phase I and in the phase II EUCALYPTUS study, showed dose proportional PK profiles with regard to maximal serum concentration (\(C_{\text{max}}\)) and area under the serum concentration-time curve from time zero to infinity (\(AUC_{\infty}\)) or the AUC within a dose interval (\(AUC_{\text{t}}\)) after the last dose, at the dose levels \(\geq 1.0\) mg/kg. Mean PK parameters for clearance and central volume of distribution were similar across the different doses, with a relatively shorter terminal half-life at dose levels \(\leq 0.5\) mg/kg, which could be attributed to target-mediated clearance at lower dose levels. Moderate drug accumulation was observed in patients who received multiple doses in the phase I study (accumulation ratio for \(AUC_{\text{t}}\) of approximately 1.2-fold for IV and 2.2-fold for SC doses).\textsuperscript{65} In the phase II EUCALYPTUS study, linear PK profiles were observed in both treatment arms, with a similar time to maximum concentrations (\(T_{\text{max}}\)) of approximately 5-6 days after both the first and the last doses. Based on mean \(C_{\text{max}}\) after last dose (\(C_{\text{max, last dose}}\) and \(AUC_{\text{t, days 5-84}}\), the drug exposure in the 300 mg + LD dose group was approximately 4.3- to 4.6-fold higher than that of the 100 mg dose group. The 300 mg + LD dose group also showed a 4-fold higher drug concentration than that of the 100 mg arm at the primary efficacy endpoint time at week 10.\textsuperscript{24}

A population PK model was developed using pooled PK data from patients enrolled in both phase I and phase II EUCALYPTUS studies as well as a subset of placebo patients in EUCALYPTUS who subsequently received 300 mg SC etrolizumab q4w in the OLE study. A 2-compartment linear model with first-order absorption and elimination kinetics adequately described the serum etrolizumab concentration-time data. Inter-patient variability for PK parameters and
residual errors were incorporated into the model. The results from the final model estimated the population typical clearance to be 0.245 L/day with a 3.2-L central volume of distribution. Inter-individual variability in the PK parameters ranged from 19% to 67%. The elimination half-life and SC bioavailability were estimated to be approximately 11 days and 53% respectively. Baseline body weight ($P < 0.001$) and serum albumin ($P < 0.001$) were found to be the only covariates significantly influencing etrolizumab clearance, yet these accounted for only 16% and 30% of the inter-individual variability in clearance, respectively. A sensitivity analysis has shown that the magnitude of effect of all statistically significant covariates on etrolizumab clearance and trough serum concentration ($C_{\text{trough}}$) at day 56 (approximate to steady state) $C_{\text{trough}}$ was low to moderate. To date, no special patient population studies (ie patients with renal or hepatic impairment or paediatric patients) have been conducted for etrolizumab.

The population PK model was used to provide simulations to support flat dosing, which demonstrated that drug exposure and variability were comparable between a body weight-based dose and a flat dose (Figure 3). The concomitant use of corticosteroid and immunosuppressant and the previous use of anti-TNF-$\alpha$ biologics were not found to have significant impact on etrolizumab PK parameters. This population PK model will be refined pending additional data from ongoing phase III studies.

### 3.2.2 Pharmacodynamics

Binding of etrolizumab to $\beta 7$ integrin receptors on the surface of circulating lymphocytes was evaluated by flow cytometry in both phase I and phase II EUCALYPTUS studies. Complete or near-complete occupancy of $\beta 7$ integrin receptors on circulating $\beta 7^{\text{High}}$ intestinal homing T and B lymphocytes was observed as early as day 2 following etrolizumab dosing. This rapid RO in the peripheral blood was observed in all dose levels (0.3-10 mg/kg IV, 0.5-3.0 mg/kg SC and 100 or 300 mg + LD SC doses) evaluated, but the duration of complete RO was dose dependent during the drug washout period in etrolizumab-treated patients.

Furthermore, a consistent PK/PD relationship was observed across etrolizumab-treated cohorts, with a minimum etrolizumab serum concentration range of 1-3 $\mu$g/mL deemed necessary for full $\beta 7$ RO on circulating $\beta 7^{\text{High}}CD45RA^-$ intestinal homing T cells. Consistent with $\beta 7$ RO in peripheral blood, complete drug occupancy of both $\alpha 4\beta 7$ and $\alpha E\beta 7$ receptors was observed in T lymphocyte subsets in colonic biopsy tissues from etrolizumab-treated patients. As expected, there was no $\beta 7$ RO in peripheral blood or in colonic tissues of patients treated with placebo.

Parallel with the observed and complete RO in peripheral blood and colonic tissue, there was a slight accumulation of $\beta 7^{\text{High}}$ intestinal homing T and B lymphocytes in peripheral blood of etrolizumab-treated patients in the phase II study. This observed peripheral accumulation of intestinal homing lymphocytes is in agreement with the etrolizumab MOA of inhibiting these lymphocytes from homing to the intestinal mucosa. Experiments using another anti-$\beta 7$ antibody that can bind $\beta 7$ in the presence of etrolizumab show that cell-surface levels of $\beta 7$ and total numbers of $\beta 7^{\text{High}}$ lymphocytes in the peripheral blood are not reduced following etrolizumab treatment, suggesting that etrolizumab-mediated blocking of cell homing to the gut is not due to downregulation of $\beta 7$ expression or the

### FIGURE 3

Prediction of steady-state $C_{\text{trough}}$ and $C_{\text{max}}$ and their variability following flat dose or body weight-based dose. Prediction of steady-state serum trough concentration ($C_{\text{trough}}$) and maximum concentration ($C_{\text{max}}$) and their variability following flat dose vs body weight-based dose. Dose scenarios simulated body weight-based dose = 1.4 mg/kg; flat dose = 100 mg. Horizontal lines in the boxes indicate the median; the top and bottom of the boxes indicate the 75th and 25th percentiles, respectively; top and bottom error bars indicate 90th and 10th percentiles, respectively; solid dots indicate outliers. Adapted from Wei et al., presented at the 2014 American College of Gastroenterology Annual Scientific Meeting; P446.
elimination of β7-expressing cells via induction of apoptosis or phagocytosis.

Although MAdCAM-1 is expressed predominantly on endothelial cells of blood vessels in the intestinal lamina propria and GALT and is overexpressed in the inflamed mucosa of patients with UC and Crohn’s disease, soluble MAdCAM-1 is detectable in peripheral blood of healthy subjects and levels declined in patients treated with etrolizumab; this was hypothesised as being potentially due to the reduced shedding of MAdCAM-1 after the interaction between α4β7 and MAdCAM-1 was blocked by etrolizumab. Etrolizumab-treated patients had significant reductions (~80% from baseline) in the levels of soluble MAdCAM-1 in the periphery at weeks 6 and 10, while no such decrease was observed in placebo-treated patients. The decrease in serum drug concentration levels during the washout period correlated with a loss in β7 RO and concurrent recovery in soluble MAdCAM-1 levels. The kinetics of serum soluble MAdCAM-1 largely mirrors the kinetic profile of the peripheral blood T lymphocytes with free β7 receptors, suggesting that serum soluble MAdCAM-1 levels may serve as an alternative marker to monitor drug occupancy of peripheral lymphocyte β7 receptor.

Unlike natalizumab, an anti-α4 mAb that has been reported to reduce serum VCAM-1 levels, serum from patients treated with etrolizumab in EUCALYPTUS showed no changes in soluble protein levels of either VCAM-1 or ICAM-1, another endothelial cell integrin ligand, compared with placebo treatment. These data further support the specificity of etrolizumab and the inference that etrolizumab is unlikely to be involved in CNS lymphocyte trafficking.

In accordance with the dual MOA of etrolizumab that modulates both homing and retention of T cells in the gut, automated cell counting of αE-stained colonic tissue sections from patients participating in the phase II EUCALYPTUS study showed a decrease in αE⁺ IELs in colonic epithelium from etrolizumab-treated patients compared with placebo controls, with no change in αEβ7⁺ cells in the lamina propria. Whether the observed decrease in αE⁺ IELs in the crypt epithelium is due to reduced retention of cells in the intraepithelial space as a result of αEβ7: E-cadherin blockade by etrolizumab or elimination of αE⁺ IELs will require additional investigation.

Despite the demonstration of significant clinical remission in the phase II EUCALYPTUS trial, not all patients who received similar exposure or therapy achieved clinical remission. Among the TNF-naïve population, who represented the majority of patients (83%) who achieved clinical remission, those treated with etrolizumab who had high αE (ITGAE) gene expression in their baseline colonic biopsies achieved a more than 2-fold higher clinical remission rate at 10 weeks compared with patients with low αE gene expression.

Similar heterogeneity in efficacy outcomes has been observed in studies using other therapies (eg anti-TNFα), suggesting a molecular and/or pathophysiological heterogeneity among patients with IBD. Efforts to understand this heterogeneity and more precise identification of patient subsets based on biomarkers such as αE may increase the likelihood of predicting clinical benefit. The current hypothesis is that patients who express αE at higher levels in their inflamed gut tissue may have an increased likelihood of achieving clinical benefit (eg achieving remission or response) with etrolizumab treatment. A careful evaluation of this hypothesis is underway during the ongoing phase III studies.

### 3.2.3 PK/PD modelling outcome

The serum etrolizumab concentration-time profile and the time profile of peripheral blood cells with free β7 receptors (available for ligand binding) from the phase I study were simultaneously modelled using a quasi-steady-state (QSS) target-mediated drug disposition (TMDD) model. The final QSS TMDD model adequately described the time profiles of both serum-free etrolizumab concentrations and peripheral T cells with free β7 receptor (% baseline [BL]) in UC patients with reasonable precision, as the relative standard error values of all parameter estimations were ≤15%.

The relationship between free serum etrolizumab concentration and peripheral T cells with free β7 receptors (% BL) was constructed using simulated PK/PD data generated by this model, and the median EC₉₀ value for peripheral T cells β7 RO (90% of baseline level) with etrolizumab was estimated as 1.3 μg/mL. The phase II EUCA-LYPTUS study dosing regimens were designed based on this estimated EC₉₀ concentration. The observed PK/PD profiles in the EUCALYPTUS study were in agreement with the model prediction (Figure 4), and the low-dose 100 mg SC q4w regimen was shown to be sufficient to fully occupy peripheral blood β7 receptors (reaching maximal pharmacological effect) in all of the treated UC patients. This dose level also demonstrated full RO in colonic biopsy tissues and clinically meaningful improvement over placebo by inducing clinical remission in patients with moderately to severely active UC. Consistent with maximised pharmacological effect at the lower 100 mg q4w dose, the higher dose regimen (300 mg + LD) did not demonstrate additional clinical benefit.

### 3.2.4 Exposure-response analysis

In the phase II EUCA-LYPTUS study, an exposure-response (E-R) relationship was evaluated using drug concentration quartile and clinical remission (at the primary endpoint). No E-R correlation was observed in this study. Although clinical remission based on the full MCS scores showed a numerically lower remission rate in the high-dose (300 mg + LD) cohort in all patients, this “inverse E-R relation” was not apparent when examining endoscopic remission rate (endoscopic score ≤1). Based on recent US Food and Drug Administration and European Medicines Agency guidance, clinical remission was reassessed with the exclusion of the physician global assessment (PGA) score from the MCS calculation. Following this adjustment in the new definition of clinical remission, the anti-TNF– naïve patient population, which had the most robust response to etrolizumab, again showed no “inverse E-R relationship” in all specified clinical outcomes (including endoscopic remission [ES ≤1], stool frequency [SF] remission, rectal bleeding [RB] remission and SF + RB remission) between the 2 dose regimens (Figure 5). Similar to these flat E-R relations for clinical outcomes, there was no correlation between...
exposure and PD changes as evidenced by a similar reduction in serum soluble MAdCAM-1 levels and full RO on peripheral \( \beta7 \) expressing T lymphocytes observed in both low- and high-dose groups.24,67,69 The lack of an E-R relationship, where "response" was either clinical readouts or PD changes, is consistent with the finding that maximal pharmacological effects were achieved in both low (100 mg q4w)- and high (300 mg + LD)-dose groups, suggesting that both dose regimens reached the plateau portion of the E-R curve. Given that all patients evaluated in the phase II EUCALYPTUS study reached full \( \beta7 \) RO in blood and gut tissue, but not all patients responded to the treatment, it is possible that other mechanisms may compensate for blockade of homing through \( \beta7 \) integrin. The relationship between maintaining \( \beta7 \) RO in blood and gut tissue and sustained clinical benefit will require further evaluation. The maintenance phase of the phase III trials will provide an opportunity to understand whether loss of the clinical benefit is associated with the loss of \( \beta7 \) RO during extended treatment. These data may offer key insights into the E-R relationship and aid in the design of long-term treatment regimens that allow for sustained and durable clinical benefit in patients with IBD.

**FIGURE 4** Comparison between observed and model-predicted PK/PD profiles at dose regimens tested in the phase II EUCALYPTUS study. Comparison between observed and model-fitted PK/PD profiles at dose regimens tested in the phase II study for (A) etrolizumab 105 mg (actual dose) at weeks 0, 4 and 8 and (B) etrolizumab 420 mg at week 0 and 300 mg at weeks 2, 4 and 8. PD, pharmacodynamics; PK, pharmacokinetics. This figure was reprinted from Wei et al.77 with permission from Wiley Periodicals, Inc.

**FIGURE 5** EUCALYPTUS Exposure-response analysis: excluding PGA component. Although clinical remission based on the full MCS showed a numerically lower remission rate at week 10 in the high-dose cohort in all patients, this "inverse-dose response" was not apparent when examining endoscopic remission (endoscopic score \( \leq 1 \)) or when the physician global assessment (PGA) score was excluded from the calculation of the MCS. Remission definitions used: MCS remission: full MCS \( \leq 2 \), with no individual subscore \( > 1 \); SF remission: SF \( \leq 1 \) and \( \geq 1 \) point decrease from baseline; RB remission: RB = 0; ES remission: ES \( \leq 1 \); Symptomatic remission: both SF and RB remission—SFRB; ES+SFRB: A composite of both SFRB and ES remission. ES, endoscopic score; MCS, Mayo Clinic Score; RB, rectal bleeding; SF, stool frequency. Adapted from Sandborn et al72 2017 European Crohn’s and Colitis Organisation Congress; P395.
3.2.5 | Therapeutic protein drug-drug interaction assessment

P450 (CYP) enzymes usually metabolise small-molecule drugs but do not impact mAb levels. Therefore, the risk for PK-based drug-drug interaction (DDI) between etrolizumab and CYP substrates is low. However, systemic inflammation as a result of disease is known to downregulate CYP enzyme expression in the liver, leading to a potential risk for DDI in patients treated with mAbs due to the anti-inflammatory nature of the pharmacological effect based on ex vivo studies. Hence, the reduction in inflammation as a result of etrolizumab treatment may increase CYP activity as well as the potential for increased metabolism of concomitant medications that are CYP substrates.

CYP3A-mediated drug metabolism is detectable in human colonic tissues, and CYP3A4 mRNA levels have been reported to correlate with CYP3A4 protein levels. Although the total content of CYP enzymes in the intestine is much lower than that in the liver, human studies have demonstrated that enteric CYP3A can contribute significantly to the first-pass metabolic effect on CYP3A substrates; in some cases, its activity may be as significant as hepatic CYP3A. Therefore, the evaluation of colonic CYP3A4 mRNA levels in the colon of patients with UC treated with etrolizumab is relevant in the context of potential DDI risk, given that the modulation of inflammatory activity in etrolizumab-treated UC is mainly localised to the colon.

CYP3A4 mRNA levels were evaluated in colonic biopsy specimens collected pre (at screening)- and post-etrolizumab or placebo treatment (at weeks 6 and 10) from patients with moderate to severe UC in the phase II EUCLYPUS study. Similar individual and mean profiles of relative CYP3A4 mRNA levels at pre- and post-treatment were observed in the active treatment arms vs the placebo arm. There was no substantial difference in the fold change (change from screening level) in CYP3A4 mRNA levels between etrolizumab and placebo treatment arms after 10 weeks of treatment, even though clinical benefit from etrolizumab was apparent by that time point. In addition, there was no correlation between disease severity, as indicated by baseline MCS, and the changes in CYP3A4 mRNA expression after treatment with etrolizumab. These data suggest that the risk for DDI with etrolizumab, as a perpetrator, on CYP3A substrate drugs appears to be low in UC patients. To date, the potential treatment effect of etrolizumab on other CYP isoforms in IBD patients has not been evaluated.

3.2.6 | Immunogenicity assessment outcome for etrolizumab

In the phase I study, 2 of 38 etrolizumab-treated patients (5%) had detectable anti-drug antibodies (ADAs) that emerged after treatment. The 2 patients who tested positive for ADAs were in the lowest dose groups (0.3 mg/kg IV single-dose and 0.5 mg/kg SC multiple-dose cohorts). Another patient had detectable ADAs at baseline; however, ADAs were not detected at any subsequent time point after etrolizumab administration for this patient. There was no observed relationship between safety and the presence of ADAs in these 2 ADA-positive patients. There were also no effects of ADAs on PK profiles.

Of 80 post-baseline–evaluable etrolizumab-treated patients with available blood samples in the phase II EUCLYPUS study, 4 (5.0%) patients, all in the etrolizumab 100 mg SC group, had detectable ADAs following treatment. One additional patient treated with etrolizumab 100 mg had detectable antibodies before receiving treatment and remained positive, with consistent titres, throughout the study. There was no observed relationship between safety and the presence of ADAs nor did positive ADAs have any apparent impact on etrolizumab serum concentrations.

In the phase II OLE SPRUCE study, treatment-induced or treatment-enhanced ADAs were detected in 6 of 108 evaluable patients (5.6%) after baseline. Two of these 6 patients were positive for ADAs during the phase II EUCLYPUS study before crossing over into SPRUCE, while the other 4 patients developed detectable ADAs during SPRUCE study (2 from the placebo group and 2 from the 100 mg SC dose group of EUCLYPUS). Again, there has been no observed relationship between safety and the presence of ADAs in SPRUCE study, including ISRs or hypersensitivity reactions.

4 | SUMMARY

Etrolizumab is currently under evaluation in phase III clinical trials for IBD. In a phase II EUCLYPUS study, etrolizumab treatment was associated with a statistically significant improvement in clinical remission rate in patients with UC compared with placebo. Etrolizumab exerts its pharmacological effect via a unique dual MOA inhibiting both lymphocyte trafficking to and retention within the intestinal mucosa. The gut-selectivity of etrolizumab results from its specific targeting of the β7 subunit of α4β7 and αEβ7 integrins, given that the ligand for αEβ7 integrin (eg MAdCAM-1) is gut predominant (expressed on endothelial cells in the blood vessels of intestinal lamina propria or in the gut-associated lymphoid tissues) and αEβ7 integrin is primarily expressed on T cells in mucosal tissues. Data from phase II EUCLYPUS study suggest that UC patients with elevated intestinal αE expression may have an increased likelihood of clinical remission in response to etrolizumab, further supporting the additional benefit of targeting αEβ7” lymphocytes.

Etrolizumab was well tolerated up to a single IV dose of 10 mg/kg or SC dose of 420 mg or 3 monthly doses of 4 mg/kg IV or 300 mg SC. The observed immunogenicity of etrolizumab was low, with about 5% of patients developing ADAs, and to date, no adverse effects or impact on drug exposure have been observed in patients with positive ADAs.

Etrolizumab has linear PK at dose levels ≥1.0 mg/kg, with significant covariate effects of serum albumin and body weight on drug clearance. Etrolizumab binds to the β7 receptor with high affinity, and with concentration-dependent duration of peripheral blood β7 RO. The median EC90 concentration for occupancy of 90% β7...
receptors (relative to baseline level) on T cells in the peripheral blood was estimated to be approximately 1.3 μg/mL. In addition, the phase II EUCLYPYTS study also demonstrated full RO in both αEβ7 and α4β7 lymphocytes in the colonic biopsies of patients treated with the 100 mg q4w SC dose regimen, indicating that the pharmacological effect was maximised at this lower dose level in UC patients. No clear E-R relationship was observed based on the analysis of clinical benefit or PD activity when etrolizumab was dosed at levels shown to achieve full RO. Etrolizumab treatment was associated with a decrease in αE+ IELs in the colonic epithelium in comparison with placebo, with no change in αE+ cells in the lamina propria. This is consistent with the hypothesised MOA of etrolizumab involving the inhibition of retention of these αE+ IELs in the gut epithelium. Other pharmacological effects of etrolizumab included decreased serum soluble MadCAM-1 protein levels and a slight increase in β7HIgP1 intestinal homing T and B lymphocytes in peripheral blood. Etrolizumab did not impact serum soluble VCAM-1 or ICAM-1 levels, unlike natalizumab that reduced serum soluble levels of VCAM-1, and did not inhibit α4β1:VCAM-1 interactions, supporting the rationale that the MOA of etrolizumab is gut-selective. The PML risk associated with natalizumab treatment due to the blockade of α4β1-mediated cell trafficking should not apply to etrolizumab therapy.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Nonclinical studies and clinical pharmacology, pharmacokinetic and pharmacodynamic analyses of etrolizumab during phase I and phase II development allowed the confirmation of the etrolizumab MOA, pharmacological activity and safety profile and the identification of recommended phase III dose regimen(s). Given the efficacy and unique gut-selective dual MOA, etrolizumab has a high potential to offer a new therapeutic option for patients with IBD as supported by a favourable benefit-risk profile. A programme of 6 phase III clinical trials with accompanying OLE components have been launched globally to evaluate the clinical efficacy of etrolizumab and gather additional safety data in patients with moderately to severely active UC or Crohn’s disease.

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AUTHORSHIP

Guarantors of the article: Meina T. Tang and Dimitry M. Danilenko.

Author contributions: MT Tang wrote sections 3, 4, and 5, critically reviewed scientific content and provided input for all other sections, and QC’d all of figure legends and citation of the references for accuracy. ME Keir wrote section 1 (including 1.1 and 1.2), reviewed scientific content and provided input for other sections. R Erickson wrote sections 2.1.1 and 3.2.6, performed experiments that generated data shown in Figures 2 and 3, and reviewed scientific content and provided input for other sections. EG Stefanich wrote section 2.2, reviewed scientific content and provided input for sections 1 and 2.1. FK Fuh wrote section 3.2.2, performed experiments that generated pharmacodynamic data shown in Figure 4, and reviewed scientific content and provided input for other sections. T. Ramirez-Montagut wrote section 3.2.2, and reviewed scientific content and provided input for section 1. JM McBride wrote sections 1 and 3.2.2, and reviewed scientific content and provided input for other sections. DM Danilenko wrote sections 1 and 2.2, and critically reviewed scientific content and provided input for all other sections. All authors have reviewed final version of this manuscript and approve the submission to AP&T for publication.

ORCID

M. T. Tang [http://orcid.org/0000-0002-4787-742X]

REFERENCES

1. Lichtenstein GR, Hanauer SB, Sandborn WJ, Practice Parameters Committee of American College of G. Management of Crohn’s disease in adults. Am J Gastroenterol 2009; 104: 465-483; quiz 4, 84.
2. Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380:1606-1619.
3. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based consensus on the diagnosis and management of Crohn’s disease: definitions and diagnosis. J Crohns Colitis. 2010;4:7-27.
4. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001;121:255-260.
5. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn’s disease in population-based cohorts. Am J Gastroenterol. 2010;105:289-297.
6. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462-2476.
7. Sandborn WJ, Colombel JF, D’Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active disease.
Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and response in patients with Crohn’s disease: results from a single-centre cohort. Gut. 2009;58:492-500.

Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Trans Gastroenterol. 2016;7:e135.

Limsrivilai J, Stidham RW, Govani SM, Waljee AK, Huang W, Higgins TANG ET AL. (2015) ET AL. 2015;31:1655-1664.

McAuliffe ME, Lanes S, Leach T, et al. Occurrence of adverse events among patients with inflammatory bowel disease in the HealthCore integrated research database. Curr Med Res Opin. 2015;31:1655-1664.

McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. Expert Rev Gastroenterol Hepatol. 2014;8:223-240.

Mehta R. Report: economic implications of inflammatory bowel disease and its management. Am J Manag Care. 2016;22(3 Suppl):s51-s60.

Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn’s disease. N Engl J Med. 2005;353:1912-1925.

Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with infliximab in 614 patients with Crohn’s disease. 2005;353:1912-1925.

Vermeire S, O’Gorman SM. Anti-integrin monoclonal antibodies. J Crohns Colitis. 2014;39:579-594.

Cepek KL, Parker CM, Madara JL, Brenner MB. Integrin alpha E beta 7 mediates adhesion of T lymphocytes to epithelial cells. J Immunol. 1993;150:3459-3470.

Briskin M, Winsor-Hines D, Shyan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. Am J Pathol. 1997;151:97-110.

Lobaton T, Vermeire S, Van Assche G, Rutgeerts P. Review article: anti-adhesion therapies for inflammatory bowel disease. Aliment Pharmacol Ther. 2014;39:579-594.

Cepek KL, Parker CM, Madara JL, Brenner MB. Integrin alpha E beta 7 mediates adhesion of T lymphocytes to epithelial cells. J Immunol. 1993;150:3459-3470.

Byron A, Humphries JD, Askari JA, Craig SE, Mould AP, Humphries MJ. Anti-integrin monoclonal antibodies. J Cell Sci. 2009;122:4009-4011.

Newham P, Craig SE, Clark K, Mould AP, Humphries MJ. Analysis of ligand-induced and ligand-attenuated epitopes on the leukocyte integrin alpha4beta1: VCAM-1, mucosal addressin cell adhesion molecule-1, and fibronectin induce distinct conformational changes. J Immunol. 1998;160:4508-4517.

Vermeire S, O’Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet. 2014;384:309-318.

Wyant T, Hedek E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis. 2016;10:1437-1444.

Hynee RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002;110:673-687.
47. Pauls K, Schon M, Kubitzka RC, et al. Role of integrin alphaE(CD103)-beta7 for tissue-specific epidermal localization of CD8+ T lymphocytes. J Invest Dermatol. 1994;103:199-208.

48. Engelhardt B, Conley FK, Klishaw PJ, Butcher EC. Lymphocytes infiltrating the CNS during inflammation display a distinctive phenotype and bind to VCAM-1 but not to MadCAM-1. Int Immunol. 1995;7:481-491.

49. Allavena R, Noy S, Andrews M, Pullen N. CNS elevation of vascular cell adhesion molecule-1 in lymphocyte interaction with endothelium and not mucosal addressin cell adhesion molecules in patients with ulcerative colitis. J Neuroimmunol. 2009;210:92-99.

50. Fuh F, Erickson R, Schlofield C, et al. Etrolizumab treatment modulates MadCAM-1 levels in serum in ulcerative colitis patients. United European Gastroenterology Week; 2016.

51. Tew GW, Hackney JA, Gibbons D, et al. Association between response to etrolizumab and expression of integrin alphaE and granzyme A in colon biopsies of patients with ulcerative colitis. Gastroenterology 2016; 150: 477-487 e9.

52. Stefaniach E, Denlenkeno DM, Wang H, et al. A humanized monoclonal antibody targeting the beta7 integrin selectively blocks intestinal homing of T lymphocytes. Br J Pharmacol. 2011;162:1855-1870.

53. Denlenkeno DM, Wang H. The yin and yang of immunomodulatory biologics: assessing the delicate balance between benefit and risk. Toxicol Pathol. 2012;40:272-278.

54. Tew JW, Schreiber S, Tang MT, Tatro AR, Oh YS, Maciuca R. Etrolizumab demonstrated no difference among doses in symptomatic and endoscopic-based evaluation of remission in anti-TNF-a naïve patients in a post-hoc analysis of the phase 2 ulcerative colitis trial (EUCALYPTUS). European Crohn’s and Colitis Organisation; 2017.

55. Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. Clin Pharmacol Ther. 2009;85:434-438.

56. Berggren S, Lennernas P, Ekelund M, Westrom B, Hoogstraate J, Lennernas H. Regional transport and metabolism of ropivacaine and its CYP3A4 metabolite PPX in human intestine. J Pharm Pharmacol. 2004;56:1593-1600.

57. Ghosh N, Chaki R, Mandal SC. Inhibition of selective adhesion molecules in treatment of inflammatory bowel disease. J Pharm Pharmacol. 2001;53:963-972.

58. Paine MF, Khalighi M, Fisher JM, et al. Characterization of intestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmaco Exp Ther. 1997;283:1552-1562.

59. Ghosh N, Chaki R, Mandal SC. Inhibition of selective adhesion molecules in treatment of inflammatory bowel disease. J Pharm Pharmacol. 2012;64:410-427.

60. Wei X, Kenny JR, Dickmann L, Macciura R, Looney C, Tang MT. Assessment of disease-related therapeutic protein drug-drug interaction for etrolizumab in patients with moderately to severely active ulcerative colitis. J Clin Pharmacol. 2016;56:693-704.