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Efficacy and Safety of Antiintegrin Antibody for Inflammatory Bowel Disease

A Systematic Review and Meta-Analysis

Lianjie Lin, MD, PhD, Xiang Liu, MD, PhD, Dongxu Wang, MD, and Changqing Zheng, MD, PhD

Abstract: We sought to evaluate the safety and efficacy of available biologics that inhibit T-cell migration by blocking $\alpha_4\beta_7$ integrins in inflammatory bowel diseases. The aim of this study is to evaluate whether Crohn disease (CD) patients receiving either vedolizumab or natalizumab have any different effect in CD Activity Index (CDAI).

Using Medline, Excerpta Medica dataBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar until October 31, 2013, we identified 10 studies examining the safety and efficacy of specific integrin inhibitors—vedolizumab, which targets an epitope comprising the $\alpha_4\beta_7$ heterodimer; natalizumab, which recognizes the α_4 integrin subunit; etrolizumab, which is specific for the β7 subunit—in the treatment of CD and ulcerative colitis (UC).

CD patients receiving either vedolizumab or natalizumab demonstrated a modest increase in remission rate, when compared with that of the placebo group. Further, although both treatments reduced the CDAI slightly, the observed clinical response was less robust than that of the remission rate. UC patients treated with vedolizumab and natalizumab were found to show more prominent increases in both remission and clinical response, compared with placebo, than patients with CD. Etrolizumab, however, was not found to significantly affect either response or remission rates in UC patients.

Biologics targeting integrins show promise as therapeutics in the treatment of inflammatory bowel disease in patients who are either nonresponsive or intolerant to traditional approaches, though further research is necessary to optimize treatment efficacies.

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Abbreviations: CD = Crohn disease, CDAI = CD activity index, CI = confidence interval, IBD = inflammatory bowel disease, MAdCAM-1 = mucosal addressin cell adhesion molecule, OR = odds ratio, PML = progressive multifocal leukoencephalopathy, UC = ulcerative colitis.

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From the Department of Gastroenterology and Hepatology (LL, XL, DW, CZ), Shengjing Hospital of China Medical University, Shenyang, China.
Correspondence: Lianjie Lin, Department of Gastroenterology and Hepatology Shengjing Hospital of China Medical University, 36 Sanhao, Heping, Shenyang 110004, China (e-mail: audreylin73@hotmail.com).
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INTRODUCTION

Crohn disease (CD) and ulcerative colitis (UC), the 2 most prevalent forms of inflammatory bowel disease (IBD), affect more than 2.5 million people of European ancestry, whereas increasing frequencies are being reported in the developing world.[1] Currently, approved therapies for IBD have considerable limitations, as they frequently display only moderate efficacy and are often associated with unacceptable risk of serious adverse events (SAEs), constituting a clear need to develop new treatment options.[2–4] Indeed, it was recently reported that 20% to 40% of CD and 40% of UC patients will ultimately prove refractive to conventional approaches using antitumor necrosis factor (anti-TNF)-α, illustrating the clear need for new treatment strategies.[5–7]

CD and UC are both characterized by persistent inflammation, which is mediated by the migration of proinflammatory T cells into the gastrointestinal tract. The repertoire of receptors expressed on the T-cell surface plays a critical role in maintaining this chronic inflammatory state. Naïve T cells encounter antigen in peripheral lymphoid organs, driving clonal expansion of effector T cells, which then migrate from the blood to affected tissues and back to the blood, creating the perpetual state of activation observed in chronic inflammatory disorders. Activated effector T cells home from the blood to affected tissues via tightly regulated cell–cell interactions. T-cell infiltration in the gut is dependent upon interactions between surface-expressed $\alpha_4\beta_7$ integrins and mucosal addressin cell adhesion molecule (MAdCAM-1), present on endothelial cells.[3,8] The critical role of this interaction in extravasation of T cells into the GI tract makes $\alpha_4\beta_7$ integrins a good target for therapy.

Several monoclonal antibodies that function to block $\alpha_4\beta_7$ integrins have been developed: natalizumab is specific for the α_4 integrin subunit (Tysabri; Biogen Idec and Elan Pharmaceuticals, Cambridge, Massachusetts, USA), vedolizumab (Entyvio, Millennium Pharmaceuticals, Cambridge, Massachusetts, USA, MLN02, LDP02, MLN0002; Millennium Pharmaceuticals) is directed against an epitope comprising the $\alpha_4\beta_7$ heterodimer, and etrolizumab (Genentech, South San Francisco, California, USA) recognizes the β7 subunit (rhuMAb β7, anti-β7, PRO145223; Genentech). Though the potential application of these molecules for the treatment of IBD is still emerging, preliminary studies suggest that they may provide efficacy for patients who are either intolerant or refractive to conventional treatment with anti-TNF-α.[7] To gain a better overview of these agents in the treatment of CD and UC, we have conducted a systematic review of randomized controlled trials to assess their relative safety and efficacy. Here, using a meta-analytical approach, we summarize and compare the current data regarding the inducement of remission and clinical responses by natalizumab, vedolizumab, and etrolizumab in IBD patients.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

In conducting this meta-analysis, we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[9] We systematically searched Medline, Embase, the Cochrane Library, and Google Scholar through October 31, 2013 for various combinations of the following keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, integrin, vedolizumab, natalizumab, etrolizumab, and monoclonal antibody. Furthermore, the reference lists of all relevant publications were searched by hand. This study did not involve human subjects, so informed consent was not required. In addition, no approval was required from any institutional review board.

Inclusion criteria for this meta-analysis required that the study be: original, excluding review articles and meta-analyses; a randomized controlled trial of an anti-$\alpha_4\beta_7$ antibody as monotherapy; participants demonstrate active IBD. Non-English publications, studies employing a single arm, and those comprising retrospective data were excluded from this analysis.

The following information was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, demographic data of subjects, regimen (dose and frequency) of anti-$\alpha4\beta7$ integrin antibody, clinical remission rate, clinical response rate, adverse events, and SAEs.

Data Extraction and Quality Assurance

Studies in this meta-analysis were identified by 2 independent reviewers using the above search strategy. Uncertainties regarding eligibility were resolved by consensus. The following information was extracted from studies that met the inclusion criteria: first author name, year of publication, study design, subject demographics (ie, age and gender), number of participants in each study, antibody and dosage for respective study groups, primary and secondary endpoints, and adverse events.

Quality assessment of all included studies was carried out using a Delphi list (Table 1).[10] This list employed 8 conditions: randomization; baseline characteristics; eligibility criteria; blinding of outcome assessor, physician, and patient; use of point estimates and variability; intention-to-treat analysis.

Outcome Measures

The primary outcome measurement was the percent of patients achieving remission, as defined by the parameters laid out by each individual study. The secondary outcomes were clinical response rates, also as defined by the primary study, and adverse events. Briefly, for the CD studies, remission was universally defined as a CD Activity Index (CDAI) score <150, whereas defined clinical response corresponded to a decrease of 70 points in CDAI in all studies, except for Sandborn et al[11], which required a decrease of 100 points in CDAI.[12–16]

For UC studies, the threshold for remission was universally defined as a Mayo Clinic score <2, with individual subscores <1. A decrease in the Mayo Clinic score >3 points, $>30\%$ from baseline, accompanied by >1 point reduction in the rectal bleeding subscore, or an absolute rectal bleeding subscore of 0–1, generally constituted clinical response.[17–20] In 1 study, however, clinical response was defined by a Mayo Clinic score reduction >2 points and 25% from baseline measurements.[20]

Statistical Analysis

The relative effect of treatment and placebo on clinical remission, response rates, and SAEs were compared and expressed as odds ratios (ORs), with 95% confidence intervals (CIs). ORs, calculated for binary outcomes, were compared between treatment and control groups. For the rate of clinical remission and response, an OR >1 indicates that the treatment group is favored, whereas for SAEs, an OR <1 indicates that the treatment group is favored (ie, associated with fewer adverse events). Study heterogeneity was identified by χ^2, using Cochran Q statistic, and quantified by I^2, which determines the percent of the total variability that cannot be ascribed to chance. For analyses in which heterogeneity ($I^2 > 50\%$) was detected, a random-effects model was used. A fixed-effects model was employed in the absence of significant heterogeneity. Pooled ORs resulting in a 2-sided P value <0.05 were considered statistically significant. Sensitivity analysis, for both

TABLE 1. Quality Assessment of Included Studies Using the Delphi List

First Author (Year)	Was a Method of Randomization Used?	Were the Groups Similar at Baseline Regarding the Most Important Prognostic Indicators?	Were the Eligibility Criteria Specified?	Was the Outcome Assessor Blinded?	Was the Care Provider Blinded?	Was the Patient Blinded?	Were Point Estimates and Measures of Variability Presented for the Primary Outcome Measures?	Did the Analysis Include an Intention-to-Treat Analysis?
CD								
Sandborn (2013)[11]	Y	Y	Y	Y	Y	Y	Y	N
Feagan (2008)[12]	Y	Y	Y	Y	Y	Y	Y	Y
Targan (2007)[13]	Y	Y	Y	Y	Y	Y	Y	N
Sandborn (2005)[14]	Y	Y	Y	Y	Y	Y	Y	Y
Ghosh (2003)[15]	Y	Y	Y	Y	Y	Y	Y	Y
Gordon (2001)[16]	Y	Y	Y	Y	Y	Y	Y	Y
UC								
Rutgeerts (2013)[17]	Y	Y	Y	Y	Y	Y	Y	N
Feagan (2013)[18]	Y	Y	Y	Y	Y	Y	Y	Y
Parikh (2012)[19]	Y	Y	Y	N	N	N	Y	N
Feagan (2005)[20]	Y	Y	Y	Y	Y	Y	Y	Y

CD = Crohn disease, UC = ulcerative colitis.

primary and secondary outcomes, was carried out using the leave-one-out approach.

Publication bias was assessed by funnel-plot analysis and Egger test. For funnel-plot analysis, the absence of publication bias was determined by assessing the ability of the data points to fit within a symmetric, funnel-shaped distribution. Evaluation by Egger linear regression was also employed, where 1-tailed *P* values >0.05 indicated a low risk of publication bias. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Literature Search, Evaluation for Study Inclusion, and Quality Assessment

As illustrated in Figure 1, initial database screens yielded 192 candidate studies. Upon further examination, 161 of these studies were found to be unsuited to the purpose of this meta-analysis, based on inclusion criteria, and were thus excluded. Twenty-one of the remaining 31 trials were also subsequently excluded, because the intervention combined antiintegrin antibodies with anti-TNF, rather than utilizing monotherapy (n = 1); the intervention failed to employ an antibody targeting any or all components of the α4β7 integrin (n = 20). The remaining 10 randomized controlled trials comprise this meta-analysis.[11–20]

The methodological approaches employed in all 10 studies were deemed to be of high quality by the Delphi list of criteria (Table 1). With the exception of Parikh et al[19], all the studies were randomized and double-blinded for assessor, provider, and patient. Four of the 10 trials did not include an intent-to-treat analysis.

Study Characteristics

A total of 10 studies are included in this report—6 focusing on CD and 4 on UC. Table 2 summarizes the baseline characteristics, which were relatively similar for each study included in this analysis. The number of study participants receiving treatment and placebo ranged from 18 to 724 (total = 1513) and 12 to 250 (total = 965), respectively. Although 4 studies in patients with CD examined the effects of natalizumab, 2 tested vedolizumab. In these studies, dosing schedules varied between those utilizing a single 300 mg dose of therapy,[11,13,14] and those using a variable concentration, which ranged from 0.5 to 6 mg/kg.[12,15,16] In addition to the dosing regimens, these studies also demonstrated variations in the frequency and absolute number of infusions. Three of the 4 studies examining efficacy of anti-α4β7 antibody in UC patients employed vedolizumab;[18–20] only Rutgeerts et al[17] tested etrolizumab. Although 1 study tested a single 300 mg dose of vedolizumab,[18] the other 2 used a variable concentration, which ranged from 0.5 to 10 mg/kg. As was noted for the CD studies, these

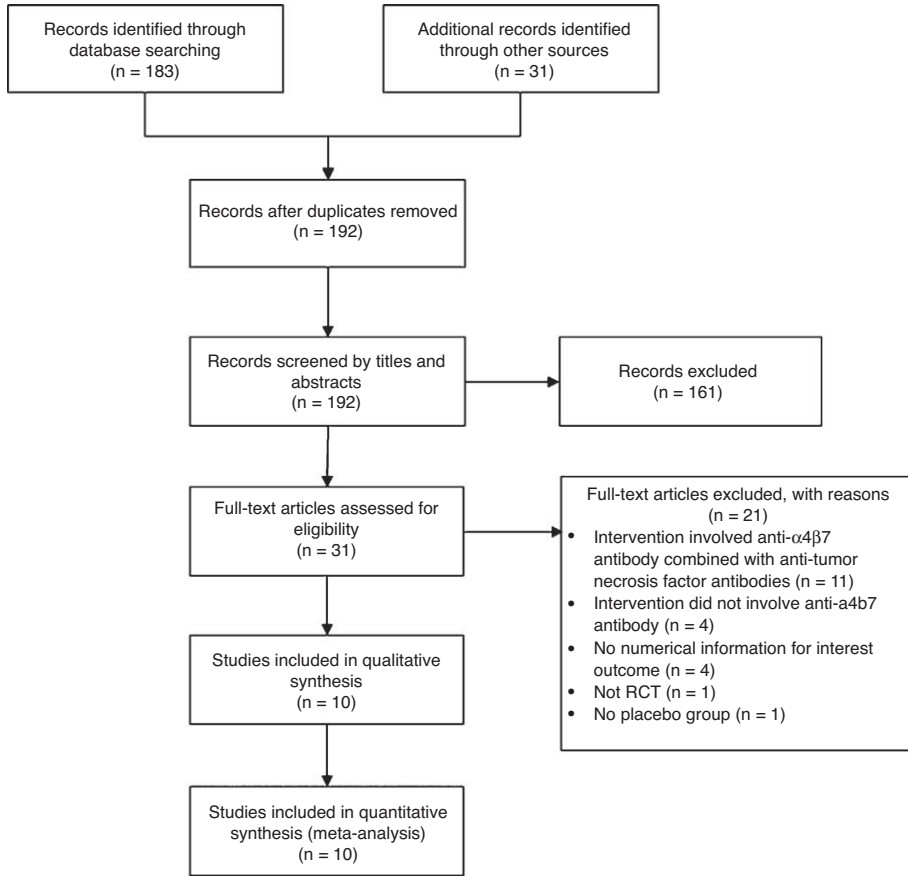


FIGURE 1. Flowchart of study selection. RCT = randomized controlled trial.

TABLE 2. Baseline Characteristics Among Studies

First Author (Year)	Study Design	Total Patient Number	Induction Period, wk	Treatment group				Placebo group		
				Intervention	Patient Number	Age (Mean ± SD, y)	Gender (% of Males)	Patient Number	Age (Mean ± SD, y)	Gender (% of Males)
CD										
Sandborn (2013)	RCT	1115	2	Vedolizumab (300 mg)	200	36.3 ± 11.6	48	148	38.6 ± 13.2	47
Feagan (2008)	RCT	185	4	Vedolizumab† (0.5 mg/kg)	62	32.0 ± 12.67	40	58	34.5 ± 11.26	52
				Vedolizumab† (2 mg/kg)	65	38.5 ± 13.07	48			
Targan (2007)	RCT	509	8	Natalizumab (300 mg)	259	38.1	41	250	37.7	41
Sandborn (2005)	RCT	905	8	Natalizumab (300 mg)	724	38 ± 12	43	181	39 ± 14	40
Ghosh (2003)	RCT	248	4	Natalizumab (1 infusion of 3 mg/kg)	68	36 (18, 66)*	40	63	34 (18, 68)*	48
				Natalizumab (2 infusion of 3 mg/kg)	66	36 (19, 64)*	45			
				Natalizumab (2 infusion of 6 mg/kg)	51	35 (19, 62)*	49			
Gordon (2001)	RCT	30	2	Natalizumab (3 mg/kg)	18	36 ± 13.2	39	12	34.4 ± 8.8	43
UC										
Rutgeerts (2013)	RCT	38	8	Etrolizumab (0.5 mg/kg, 1.5 mg/kg, 3 mg/kg, 4 mg/kg)	18	44 ± 14	72	5	39 ± 19	60
Feagan (2013)	RCT	895	2	Vedolizumab (300 mg)	225	40.1 ± 13.1	59	149	41.2 ± 12.5	62
Parikh (2012)	RCT	46	12	Vedolizumab (2 mg/kg, 6 mg/kg, 10 mg/kg)	37	41 (19, 69)*	43	9	33 (21, 51)*	33
Feagan (2005)	RCT	181	4	Vedolizumab‡(0.5 g/kg)	58	41.6 ± 14.7	57	63	38.9 ± 13.4	56
				Vedolizumab‡ (2.0 mg/kg)	60	43.8 ± 14.6	50			

CD = Crohn disease, RCT = randomized controlled trial, UC = ulcerative colitis.
* Mean (minimum, maximum)
† MLN0002 in primary source.
‡ MLN02 in primary source.

treatment schedules varied both in frequency and number (data not shown). Primary and secondary outcomes for all studies are summarized in Table 3. It should be noted that more patients were evaluated for adverse events than were assessed for primary and secondary outcomes. Sandborn (2013)[11] and Feagan (2013)[18] both included 2 cohorts to assess safety, which resulted in the disparity.

Efficacy of Anti-α4β7 Antibody

Six studies in CD patients were compared with regard to the primary outcome of clinical remission. Because there was evidence of moderate heterogeneity within these studies (Q statistic = 10.99, $I^2 = 54.50\%$, $P = 0.052$), a random-effects model was applied. The difference in the clinical remission rate favored the treatment group over placebo (OR 2.108, 95% CI 1.460–3.043, $P < 0.001$) (Figure 2A). Five of the 6 studies involving CD patients were included in the analysis of clinical response rates. As shown in Figure 2B, treatment resulted in a higher frequency of clinical response than that observed for the placebo control (OR 1.607, 95% CI 1.327–1.9473, $P < 0.001$). Because there was no evidence of heterogeneity in these 5 studies (Q statistic = 6.15, $I^2 = 34.99\%$, $P = 0.188$), a fixed-effects model was applied.

TABLE 3. Summary of the Clinical Remission Rate, Clinical Response Rate, and SAEs

First Author (Year)	Time Point of Efficacy Evaluation, wk	Treatment group			Placebo group			Time Point of Safety Evaluation	Treatment Group		Placebo Group	
		n	Clinical Remission Rate, %	Clinical Response Rate, %	n	Clinical Remission Rate, %	Clinical Response Rate, %		n	Any SAE, %	n	Any SAE, %
CD												
Sandborn (2013)	6	200	15	31	148	7	26	12 mo	814	24	301	15
Feagan (2008)	8	127	34	50	58	21	41	3 mo	127	13	58	17
Targan (2007)	12	259	38	60	250	25	44	3 mo	259	5	250	10
Sandborn (2005)	10	724	37	56	181	30	49	10 wk	723	7	181	7
Ghosh (2003)	6	185	61	63	63	27	38	3 mo	181	11	63	11
Gordon (2001)	2	18	39	n/a	12	8	n/a	3 mo	18	n/a	12	n/a
UC												
Rutgeerts (2013)	10	38	17	67	10	20	80	20 wk	38	18	10	10
Feagan (2013)	6	225	17	47	149	5	26	12 mo	620	12	275	14
Parikh (2012)	16	37	n/a	73	9	n/a	32	9 mo	37	5	9	0
Feagan (2005)	6	118	32	59	63	14	33	6 wk	118	15	63	10

CD = Crohn disease, n = number of patients, n/a = not available, SAE = serious adverse events, UC = ulcerative colitis.

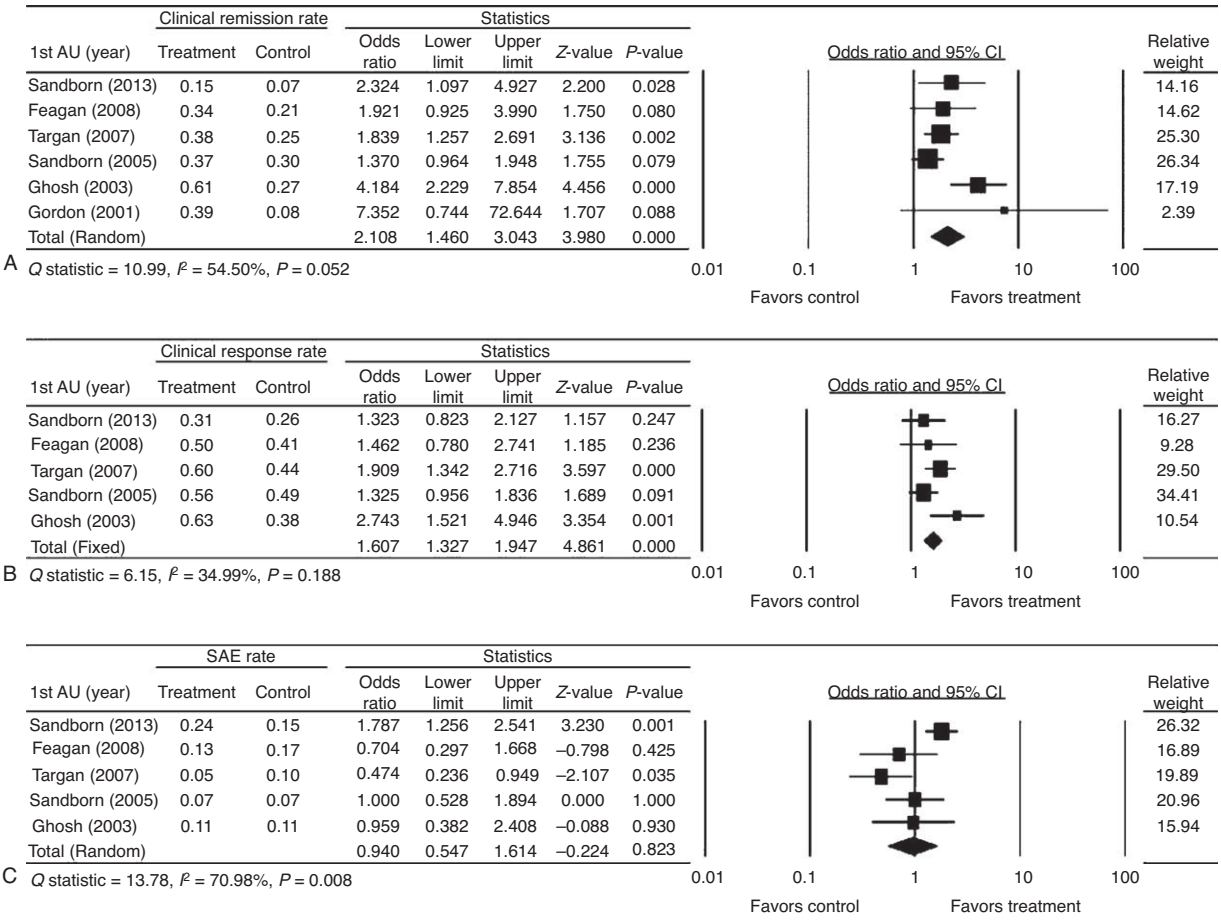


FIGURE 2. Efficacy and safety of anti-α4β7 antibody in the treatment of CD. Forest plot comparing the effect of anti-α4β7 antibodies on (A) the clinical remission rate, (B) the clinical response rate, and (C) the SAEs rate versus placebo control. 1st AU = first author, CD = Crohn disease, CI = confidence interval, Lower limit = lower bound of the 95% CI, Upper limit = upper bound of the 95% CI, SAE = serious adverse events.

Three of the 4 studies in UC patients were included for analysis of clinical remission (Figure 3A). Because no heterogeneity was detected, a fixed-effects model was applied (Q statistic = 2.28, $I^2 = 12.42\%$, $P = 0.319$). The difference in clinical remission rate between the treatment and placebo groups showed a clear advantage in patients receiving antibody (OR 2.839, 95% CI 1.656–4.867, $P < 0.001$) (Figure 3A). For analysis of clinical response rates, all 4 of UC studies were included. Again, a fixed-effects model was employed, as there was no evidence of heterogeneity among the studies (Q statistic = 4.75, $I^2 = 36.80\%$, $P = 0.191$). Patients receiving treatment were found to demonstrate a higher frequency of clinical responses than those receiving placebo (OR 2.609, 95% CI 1.836–3.709, $P < 0.001$) (Figure 3B).

Safety of Anti-α4β7 Antibody

Five of the 6 studies focused on CD were assessed with regard to SAEs associated with treatment (Figure 2C). Evidence of significant heterogeneity between the studies resulted in use of a random-effects model (Q statistic = 13.78, $I^2 = 70.98\%$, $P = 0.008$). No significant difference was detected in the SAE rate of the treatment group, when compared with that of the placebo control group (OR 0.940, 95% CI 0.547–1.614, $P = 0.823$) (Figure 2C). As no heterogeneity was detected among the 4 UC studies included for analysis of SAE, a fixed-effects model was applied (Q statistic = 0.56, $I^2 = 0\%$, $P = 0.905$). As was observed for CD patient groups, treatment did not significantly affect the rate of SAE, compared with control, in studies of UC patients (OR 0.953, 95% CI 0.647–1.403, $P = 0.807$) (Fig. 3C).

A summary of adverse events reported by studies included in this meta-analysis is shown in Table 4. The most commonly reported adverse events were exacerbation of disease (ie, CD or UC) and headache. As mentioned previously, however, these effects were not found to be significantly different in the treatment group, compared with the control group. Additional reported adverse events, including nausea, infections, fatigue, and nasopharyngitis were also found to occur at similar rates between treatment and control groups. There was a higher frequency of adverse events in patients with CD than in those with UC. Overall, however, all treatments were found to be well tolerated.

Sensitivity Analysis and Publication Bias

To evaluate the reliability of our meta-analytical data, we tested sensitivity using the 'leave-one-out' approach. As shown in Figure 4A, removal of any 1 study from the analysis of remission rates in CD patients does not significantly affect the

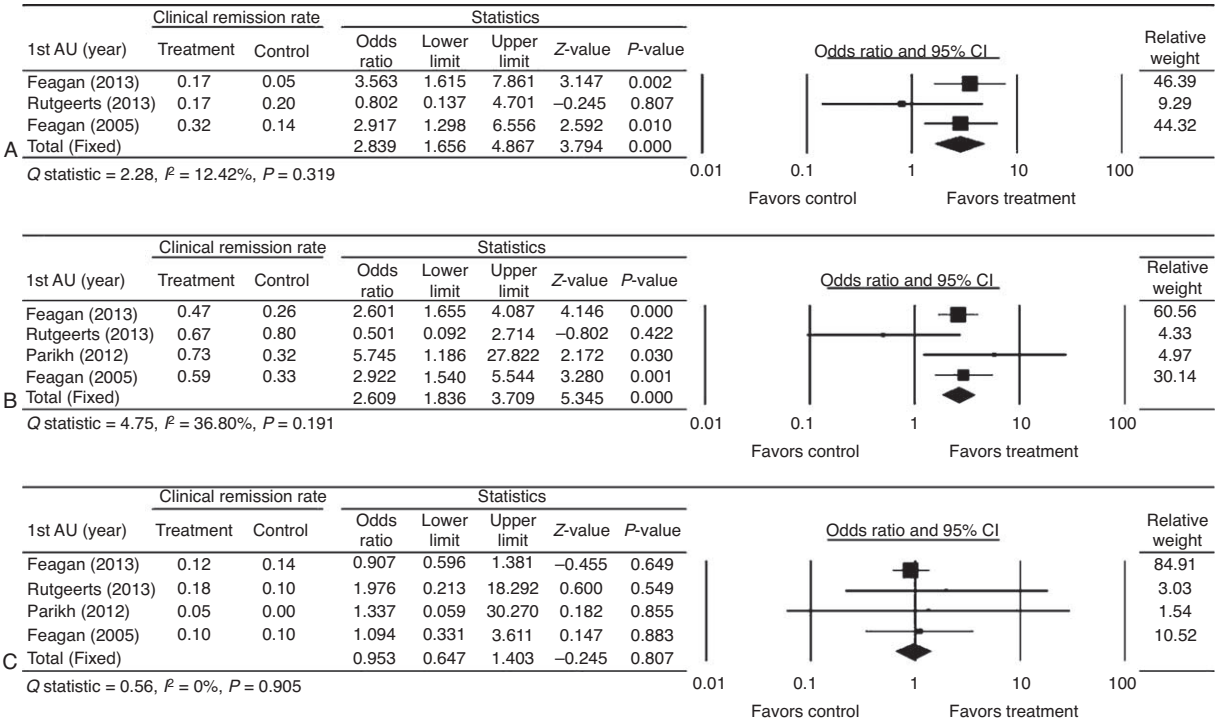


FIGURE 3. Efficacy and safety of anti-α4β7 antibody in the treatment of UC. Forest plot comparing the effect of anti-α4β7 antibodies on (A) the clinical remission rate, (B) the clinical response rate, and (C) the SAEs rate versus placebo control. 1st AU = first author, CI = confidence interval, Lower limit = lower bound of the 95% CI, SAE = serious adverse events, UC = ulcerative colitis, Upper limit = upper bound of the 95% CI.

outcome. Similarly, no one study was found to disproportionately influence the results obtained for remission rates in UC patients (Figure 4B). The constancy in direction and magnitude of the combined estimates, regardless of exclusion of individual studies, indicates that the meta-analysis had good reliability.

To ensure that there was no publication bias for this analysis, we employed Egger test. This test found no evidence of publication bias for clinical remission rates in either the CD studies (Figure 5A; $t = 1.88$, $P = 0.068$) or the UC studies (Figure 5B; $t = 4.93$, $P = 0.064$).

DISCUSSION

A large percentage of patients with moderate-to-severe IBD demonstrate refractory disease, either completely unresponsive to standard treatment regimens or unable to mount a durable response.[2–4] Gut infiltration by T lymphocytes is well established as a mechanism of IBD pathogenesis. The molecular pathways that mediate this migration of lymphocytes into the GI tract is tightly regulated, involving coordinated interactions between several adhesion and signaling molecules (eg, selectins, integrins, and chemokine receptors), expressed on the T-cell surface, with their corresponding ligands, on endothelial cells. Gut infiltration by T cells specifically requires interactions between surface-localized $\alpha_4\beta_7$ integrins and MAdCAM-1, expressed on the surface of endothelial cells.[21] Disruption of this interaction has been demonstrated by several antibodies targeting $\alpha_4\beta_7$ integrins.[22,23]

Here, we showed that antibody-mediated inhibition of $\alpha_4\beta_7$ integrins significantly increased both the rates of clinical remission and response in patients with either CD or UC. These antibody treatments were well tolerated, demonstrating a similar risk of developing SAE to that of the placebo controls. Interestingly, we found the antibodies to elicit a more consistent response in CD than in UC (Figures 2 and 3). The 1 exception to this observation was Rutgeerts (2013), which assessed efficacy of etrolizumab and showed greater efficacy in patients with UC. These differences may arise from variation in the moieties within $\alpha_4\beta_7$ heterodimer targeted by the respective antibodies, though it is difficult to examine with any accuracy, as the number of patients treated with etrolizumab only represent 1.97% of the total number of patients assessed in this review. Further studies will be necessary to evaluate whether there is a difference in efficacy for antiintegrin therapies in the treatment of CD versus UC.

Although vedolizumab specifically recognizes an epitope comprising both subunits of the $\alpha_4\beta_7$ integrin, natalizumab is more generalized, targeting only the α_4 subunit. Because natalizumab targets α_4, inhibition is not limited to $\alpha_4\beta_7$ heterodimers, but affects interactions between $\alpha_4\beta_1$ and vascular cell adhesion molecule-1 in the central nervous system. This additional effect is believed to play a role in the development of a devastating neurological disorder, progressive multifocal leukoencephalopathy (PML), in a small cohort of patients receiving natalizumab.[24] Recently, a retrospective study found the risk of PML among natalizumab-treated patients to be directly linked to 3 factors: the presence of anti-John Cunningham virus antibodies, prior exposure to immunosuppressive drugs, and the duration of natalizumab treatment.[25] Although no patients in the studies examined here developed PML, the risk associated with natalizumab presents a clear advantage for the use of vedolizumab and etrolizumab. Though emergent

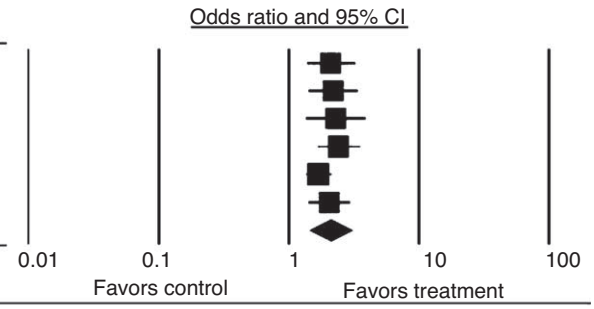
TABLE 4. Summary of Adverse Events*

First Author (Year)	Group	Patient Numbers	CD or UC Exacerbation	Infections	Headache	Abdominal Pain	Nausea	Vomiting	Fatigue	Arthralgia	Pyrexia	Influenza-Like Illness	Nasopharyngitis	Upper Respiratory Tract Infection	Cough	Anemia	Hypertension	C-reactive Protein Increased	Constipation	Dizziness	Colitis	Frequent Bowel Movements	Rash	Urinary Tract Infection	Blood in Stool	Pain	Back Pain
CD																											
Sandborn (2013)	Tx	814	20.1	5.5	11.9	—	11.1	6.0	6.5	13.5	12.7	—	12.3	6.6	—	—	—	—	—	—	—	—	—	—	—	—	4.7
	Placebo	301	21.6	3.0	15.6	—	10.0	7.6	4.7	13.3	13.3	—	8.0	5.6	—	—	—	—	—	—	—	—	—	—	—	—	4.0
Feagan (2008)	Tx	127	19	1	36	15	18	—	18	—	11	—	15	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Placebo	58	19	3	24	19	12	—	19	—	7	—	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Targan (2007)	Tx	259	7	35	29	12	15	—	10	—	—	—	11	—	—	—	—	—	—	10	—	—	—	—	—	—	—
	Placebo	250	13	30	21	9	12	—	7	—	—	—	6	—	—	—	—	—	—	8	—	—	—	—	—	—	—
Sandborn (2005)	Tx	723	6	49	30	11	17	8	10	—	—	—	14	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Placebo	181	10	43	23	13	17	10	8	—	—	—	14	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Ghosh (2003)	Tx	181	—	10	31	15	9	—	—	10	—	14	10	—	—	—	—	—	—	—	13	—	—	—	—	9	—
	Placebo	63	—	13	32	17	16	—	—	11	—	8	8	—	—	—	—	—	—	—	14	—	—	—	—	8	—
Gordon (2001)	Tx	18	39	—	50	22	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Placebo	12	42	—	50	17	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
UC																											
Rutgeerts (2013)	Tx	38	42	45	32	16	13	—	16	11	—	—	16	5	—	—	—	—	—	13	—	—	—	11	—	—	5
	Placebo	10	80	40	20	10	10	—	0	0	—	—	20	20	—	—	—	—	—	10	—	—	—	0	—	—	20
Feagan (2013)	Tx	620	15.6	1.9	12.9	5.6	6.1	—	5.3	9.0	—	—	12.9	8.4	5.8	—	—	—	—	—	—	—	—	—	—	—	—
	Placebo	275	21.1	2.9	10.2	3.6	6.9	—	3.6	9.1	—	—	9.5	7.6	4.7	5.8	—	—	—	—	—	—	—	—	—	—	—
Parikh (2012)	Tx	37	8	—	19	—	—	—	—	—	5	5	8	8	5	—	5	3	3	3	—	—	—	—	—	—	—
	Placebo	9	44	—	11	—	—	—	—	—	0	0	11	33	0	—	0	11	11	11	—	—	—	—	—	—	—
Feagan (2005)	Tx	118	43	3	19	9	22	7	11	9	—	—	14	—	—	—	—	—	—	8	—	13	8	—	8	—	—
	Placebo	63	38	0	21	13	16	8	11	8	—	—	8	—	—	—	—	—	—	2	—	16	6	—	13	—	—

CD = Crohn disease, UC = ulcerative colitis.
* Data presented as percentage (%).

A

1st AU (year)	Statistics: Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Sandborn (2013)	2.104	1.369	3.235	3.390	0.001
Feagan (2005)	2.184	1.408	3.390	3.484	0.000
Targan (2007)	2.299	1.362	3.880	3.115	0.002
Sandborn (2005)	2.418	1.656	3.530	4.573	0.000
Ghosh (2003)	1.688	1.340	2.125	4.448	0.000
Gordon (2001)	2.041	1.415	2.943	3.817	0.000
Total (Random)	2.108	1.460	3.043	3.980	0.000



B

1st AU (year)	Statistics: Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Feagan (2013)	2.332	1.117	4.870	2.255	0.024
Rutgeerts (2013)	3.231	1.835	5.691	4.062	0.000
Feagan (2005)	2.778	1.349	5.721	2.772	0.006
Total (Fixed)	2.839	1.656	4.867	3.794	0.000

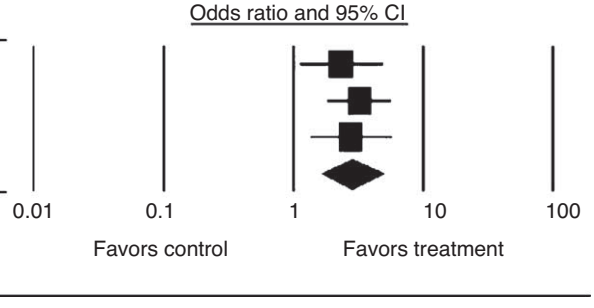


FIGURE 4. Evaluation of meta-analysis sensitivity by the 'leave-one-out' approach. Clinical remission rate in (A) pooled CD studies, and (B) pooled UC studies, neglecting the specified trials. CD = Crohn disease, CI = confidence interval, Lower limit = lower bound of the 95% CI, UC = ulcerative colitis, Upper limit = upper bound of the 95% CI.

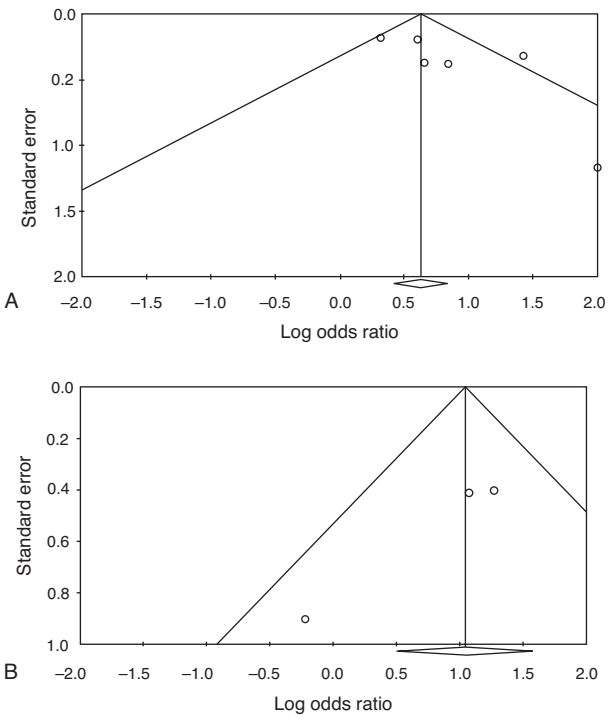


FIGURE 5. Funnel plots for clinical remission rate in (A) CD and (B) UC. CD = Crohn disease, UC = ulcerative colitis.

biologics targeting $\alpha_4\beta_7$ have been previously reviewed, the rapidly changing nature of this field, coupled with the high volume of recent and ongoing clinical trials, demand further examination of the data.[26,27]

The results obtained in this meta-analysis, although promising, suffer from several caveats. Specifically, there was significant clinical heterogeneity associated with variation in the treatment regimens used (eg, therapy, duration, dosage). Furthermore, included studies only investigated anti-$\alpha4\beta7$ monotherapy, rather than in conjunction with conventional IBD treatment strategies. It would be interesting to determine the safety and efficacy of such therapeutics in combination with other drugs, including immunosuppressants, anti-TNF antibodies, and other antibodies targeting proinflammatory cytokines.

Up to 40% of all UC and CD patients will prove refractive to conventional IBD treatment regimens.[7] New approaches exploiting integrin-mediated extravasation of effector T cells could address this significant treatment gap. Furthermore, conventional therapies, such as anti-TNF and methotrexate, are associated with significant adverse events.[28–31] Our study showed that antibodies specific for $\alpha4\beta7$ integrins safely increased both the rates of clinical remission and response in both CD and UC patients. Evaluation of these therapies in a real-world setting, as well as in combination with other agents, will help to better assess their efficacy and safety relative to conventional approaches, such as anti-TNF-α. Regardless, antibodies aimed at blocking the chronic inflammation that is characteristic of IBD show enormous promise and represent a new era in therapeutics for immune-mediated disorders.

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