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META-ANALYSIS

Integrin antagonists are effective and safe for Crohn's disease: A meta-analysis

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Abstract

AIM: To evaluate the efficacy and safety of integrin antagonists, including natalizumab and vedolizumab, in Crohn's disease (CD).

METHODS: We carried out a literature search in PubMed, MEDLINE, EMBASE and the Cochrane Library to screen for citations from January 1990 to August 2014. Data analysis was performed using Review Manager version 5.2.

RESULTS: A total of 1340 patients from five studies were involved in this meta-analysis. During 6-12 wk treatment, integrin antagonists increased the rate of clinical response and remission with OR = 1.69, 95%CI: 1.37-2.09 and 1.84, 95%CI: 1.44-2.34, respectively. No significant difference was found between integrin antagonists and placebo treatments regarding their adverse reactions (OR = 1.07, 95%CI: 0.83-1.38) and serious adverse reactions (OR = 0.81, 95%CI: 0.57-1.15).

CONCLUSION: The results prove the efficacy and safety of integrin antagonists for CD treatment, although the treatment strategies varied.

Key words: Crohn's disease; Drug efficacy; Integrin antagonist; Meta-analysis; Drug safety

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Core tip: Integrin antagonists were used to treat Crohn's disease (CD), but their efficacy and safety are not yet certain. We performed this systematic review and meta-analysis to evaluate the efficacy and safety of integrin antagonists, including natalizumab and vedolizumab, in CD. During 6-12 wk treatment, integrin antagonists increased the rate of clinical response and remission. There was no significant difference between integrin antagonists and placebo regarding their adverse reactions and serious adverse reactions. These results prove the efficacy and safety of integrin antagonists for CD treatment.

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INTRODUCTION

Crohn's disease (CD) is a relapsing systemic inflammatory disease that commonly affects the gastrointestinal tract, with extraintestinal manifestations and associated immune disorders[1]. CD often leads to abdominal pain, fever, malaise, fatigue, diarrhea, fistula formation, bowel obstruction, and malnutrition. The common therapies for CD are aminosalicylates, steroids, immunosuppressants and monoclonal antibodies[2]. Aminosalicylates such as mesalamine and sulfasalazine are used to treat mild to moderate CD[3], while corticosteroids are used to treat acute active CD and patients who do not response to aminosalicylates[4]. However, the use of corticosteroids has a high risk of Cushing's syndrome, infection and diabetes in the short term, and bone loss, increased ocular pressure and diabetes in the long term[5]. Immunosuppressants are used to inhibit inflammation. Long-term use of immunosuppressants may cause infection, liver toxicity and bone marrow suppression[6]. Biologic agents used to treat CD mainly consist of tumor necrosis factor (TNF)-α inhibitors and α-integrin antagonists.

Natalizumab and vedolizumab are the integrin antagonists approved by the United States Food and Drug Administration. Natalizumab is a monoclonal antibody antagonizing α4β1 and α4β7 intergrin-mediated interactions in the gut and brain[7]. It is effective in treating CD but is limited by increasing the risk of progressive multifocal leukoencephalopathy (PML)[8]. Vedolizumab is a humanized IgG1 monoclonal antibody for α4β7 integrin. It only regulates gut lymphocyte trafficking, therefore, it is not likely to cause PML[9].

Previous studies have indicated the efficacy of integrin inhibitors in CD therapy. However, the sample size of those studies was small. Therefore, we performed a meta-analysis including current double-blind randomized controlled trials (RCTs) to evaluate the efficacy of integrin antagonists for CD treatment.

MATERIALS AND METHODS

Search strategy and inclusion criteria

EMBASE, MEDLINE, PubMed and Cochrane Library were searched for RCTs from January 1990 to August 2014. The key words "Crohn disease" and "natalizumab" or "MLN0002" or "vedolizumab" were used in screening relevant citations. The inclusion criteria were: (1) RCTs; and (2) studies provided data for at least one of the main outcomes, including rate of clinical response, rate of clinical remission, common adverse reactions, and serious adverse reactions. Clinical remission was defined as Crohn's Disease Activity Index (CDAI) score < 150 and clinical response was defined as a decrement of ⩾ 70 points in CDAI score from baseline (week 0).

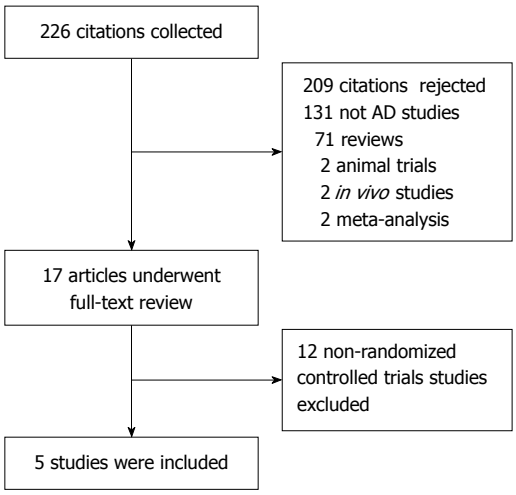

Figure 1 Flow diagram of the studies identified.

Data extraction and quality assessment

The following information was extracted from each study: first author name; year of publication; number of patients; rate of clinical response; rate of clinical remission; number of common adverse reactions; and number of serious adverse reactions. The Jadad score was used to assess the quality of included studies. Studies with score ⩾ 3 were regarded as high-quality RCTs, while studies with score < 3 were defined as low-quality RCTs.

Statistical analysis

Data analysis was performed using RevMan version 5.2 for each individual study, and dichotomous data were reported as OR with 95%CI. Heterogeneity among studies was assessed by Cochrane *Q* statistics and I^2 test. A significant level of ⩾ 50% for I^2 test was considered as evidence of heterogeneity. A fixed-effect model was used when there was no evidence of heterogeneity, otherwise a random-effect model was chosen. Ghosh *et al*[10] used three different treatment strategies and Feagan *et al*[11] used two. Each treatment strategy was regarded as a single treatment group. All of the treatments were analyzed together.

RESULTS

Search results and characteristics

A total of 226 citations were obtained *via* database searches, and five met the inclusion criteria (Figure 1). A total of 1340 patients were involved; 462 were treated with natalizumab, 347 with vedolizumab, and 531 with placebo. The information in these citations is summarized in Table 1. All five studies had a Jadad score ⩾ 3 (Table 1).

Table 1 Main characteristics of the included studies

Ref.	Study duration	Treatment	Age (mean, yr)	Disease duration (yr)	Baseline CDAI (mean)	Jadad score
Gordon *et al*[12], 2001	12	Natalizumab 3 mg/kg intravenous infusion at 0 wk, n = 18	36	8.5	258	5
		Placebo intravenous infusion at 0 wk, n = 12	34	8.4	273	
Ghosh *et al*[10], 2003	12	Natalizumab 6 mg/kg intravenous infusion at 0, 4 wk, n = 51	35	7.8	298	5
		Natalizumab 3 mg/kg intravenous infusion at 0, 4 wk, n = 66	36	8.1	300	
		Natalizumab 3 mg/kg intravenous infusion at 0 wk, n = 68	36	8.4	288	
		Placebo intravenous infusion at 0, 4 wk, n = 63	34	8.9	300	
Targan *et al*[13], 2007	12	Natalizumab 300 mg intravenous infusion at 0, 4, 8 wk, n = 259	38	10.1	304	5
		Placebo intravenous infusion at 0, 4, 8 wk, n = 250	38	10	300	
Feagan *et al*[11], 2008	8	Vedolizumab 2 mg/kg intravenous infusion at 0, 4 wk, n = 65	39	8	297	5
		Vedolizumab 0.5 mg/kg intravenous infusion at 0, 4 wk, n = 62	36	8.8	288	
		Placebo intravenous infusion at 0, 4 wk, n = 58	35	9	288	
Sandborn *et al*[14], 2013	6	Vedolizumab 300 mg intravenous infusion at 0, 2 wk, n = 220	36	9.2	327	5
		Placebo intravenous infusion at 0, 2 wk, n = 148	39	8.2	325	

CDAI: Crohn's disease activity index.

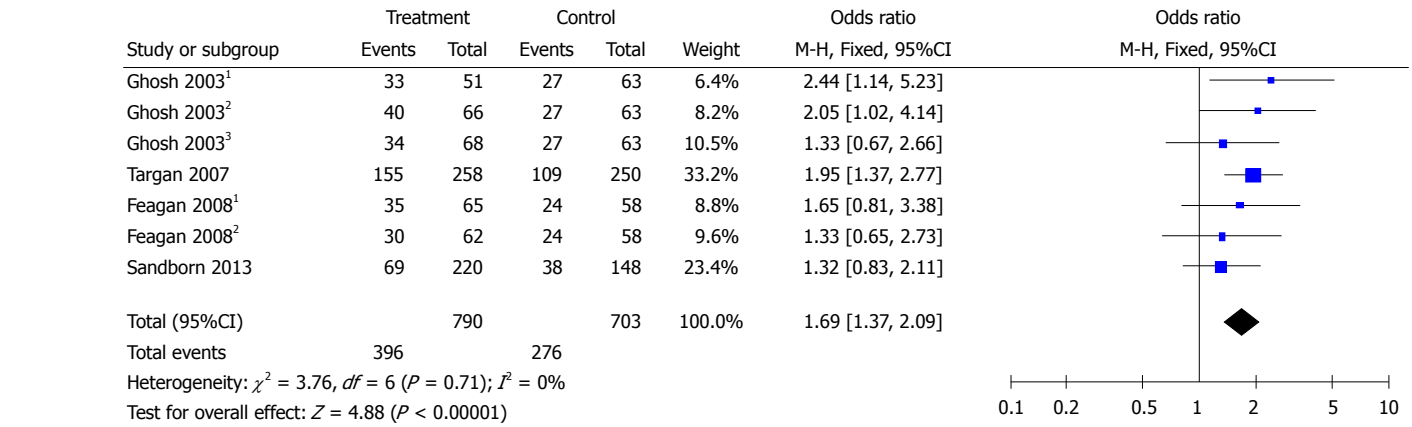

Figure 2 Forest plots of clinical response. Clinical response was defined as a decrement of ⩾ 70 points in CDAI score from baseline (week 0). Ghosh 2003[1]: 6 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[2]: 3 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[3]: 3 mg/kg natalizumab at 0 wk. Feagan 2008[1]: 2 mg/kg vedolizumab at 0 and 4 wk; Feagan 2008[2]: 0.5 mg/kg vedolizumab at 0 and 4 wk.

Clinical response

Clinical response was reported in four studies. According to the results of the meta-analysis, integrin antagonists increased the clinical response to CD. The OR for clinical response was 1.69 (95%CI: 1.37-2.09). There was no heterogeneity as I^2 = 0% (Figure 2).

Clinical remission

Clinical remission was reported in five studies. Integrin antagonists had a higher rate of remission than placebo. The OR for clinical remission was 1.84 (95%CI: 1.44-2.34). There was no heterogeneity as I^2 = 0% (Figure 3).

Safety

Natalizumab and vedolizumab were both well tolerated during treatment. They had similar rates of common adverse reactions (OR = 1.07, 95%CI: 0.83-1.38) and serious adverse reactions (OR = 0.81, 95%CI: 0.57-1.15) compared to placebo (Figures 4 and 5).

DISCUSSION

The incidence of CD is increasing worldwide, with more young patients, and it requires life-long medical and surgical input[15]. Over the past few decades, TNF-α inhibitors such as infliximab, adalimumab,

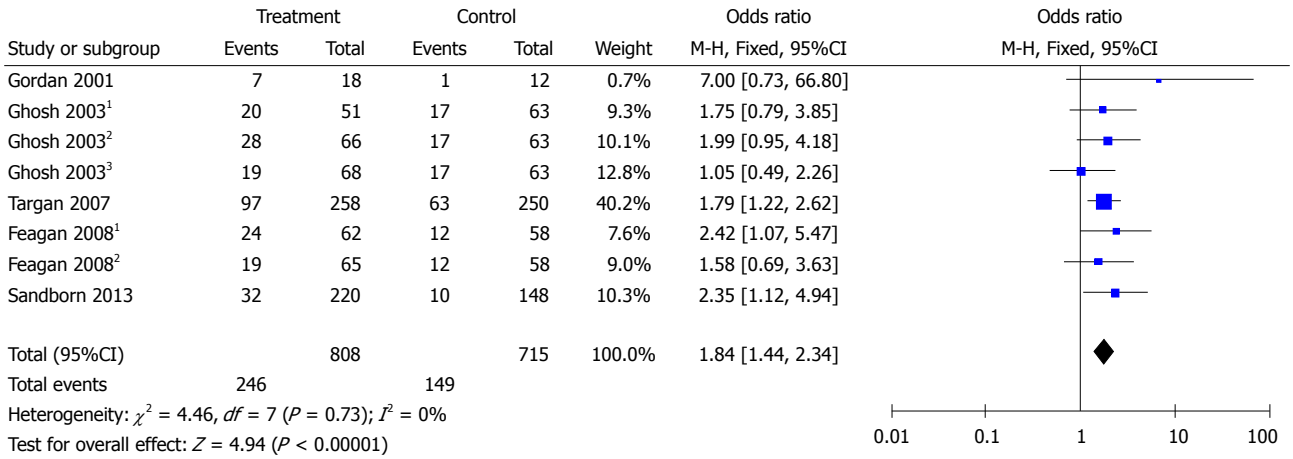

Figure 3 Forest plots of clinical remission. Clinical remission was defined as CDAI score < 150. Ghosh 2003[1]: 6 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[2]: 3 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[3]: 3 mg/kg natalizumab at 0 wk. Feagan 2008[1]: 2 mg/kg vedolizumab at 0 and 4 wk; Feagan 2008[2]: 0.5 mg/kg vedolizumab at 0 and 4 wk.

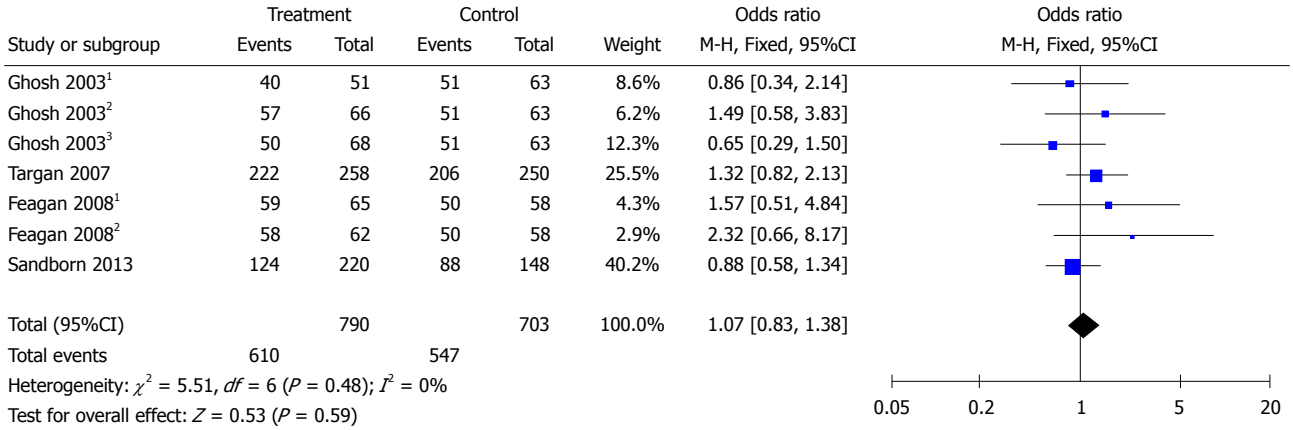

Figure 4 Forest plots of common adverse reactions. Ghosh 2003[1]: 6 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[2]: 3 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[3]: 3 mg/kg natalizumab at 0 wk. Feagan 2008[1]: 2 mg/kg vedolizumab at 0 and 4 wk; Feagan 2008[2]: 0.5 mg/kg vedolizumab at 0 and 4 wk.

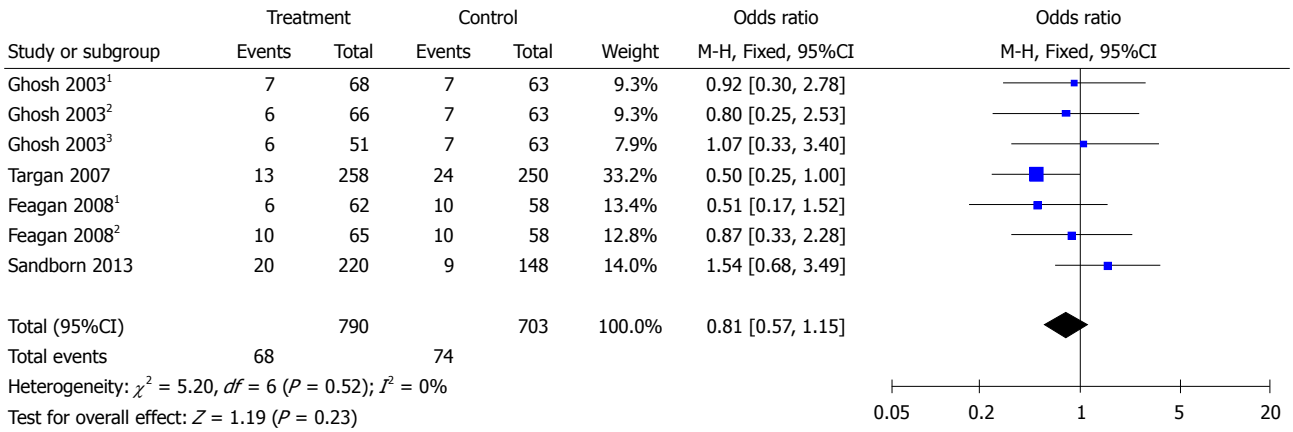

Figure 5 Forest plots of serious adverse reactions. Ghosh 2003[1]: 6 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[2]: 3 mg/kg natalizumab at 0 and 4 wk; Ghosh 2003[3]: 3 mg/kg natalizumab at 0 wk. Feagan 2008[1]: 2 mg/kg vedolizumab at 0 and 4 wk; Feagan 2008[2]: 0.5 mg/kg vedolizumab at 0 and 4 wk.

certolizumab pegol, and golimumab have been used in patients with moderate to severe CD who failed to respond to corticosteroids[16]. TNF-α inhibitors have been proved effective in CD treatment, however 40% of patients will lose their response to them at a rate of 10%-13% per year[17]. This led to the search for an alternative way to treat CD. It was found that the migration of leukocytes and other inflammatory

cells into the intestinal vasculature and disruption of intestinal barrier function were important in the pathogenesis of CD[18]. The integrin antagonists (natalizumab and vedolizumab) aim to block the interaction between leukocytes and endothelial cells to inhibit inflammation[19]. One RCT showed that vedolizumab can lead to clinical remission at 10 wk in patients who failed TNF antagonist treatment[20].

Our meta-analysis suggested that short-term treatment with integrin antagonists could improve the clinical response and remission in CD patients. Compared to placebo, patients treated with 6 mg/kg natalizumab at 0 and 4 wk showed the highest OR for clinical response (OR = 2.44, 95%CI: 1.14-5.23), followed by 3 mg/kg natalizumab at 0 and 4 wk (OR = 2.05, 95%CI: 1.02-4.14). However, there was no significant difference between natalizumab and vedolizumab in terms of clinical response and remission.

According to meta-analysis results, integrin antagonists had a similar rate of adverse reactions as the placebo group. Previous studies showed that natalizumab could increase the risk of PML at a rate of 0.09-11 per 1000 patients[8]. Vedolizumab was designed to target the $\alpha4\beta7$ integrin heterodimer and cannot cross the blood-brain barrier[21]. There are no reported cases of PML in patients treated with vedolizumab for CD[22]. However, we did not find PML reported in the included studies and compared to placebo, both natalizumab and vedolizumab had a similar rate of serious adverse reactions.

There were some limitations to our study. The treatment strategies were different for each study. For example Ghosh *et al*[10] used 3 mg/kg natalizumab, while Targan *et al*[13] used a fix dose of 300 mg. The duration of treatment also varied. The inclusion criteria differed among the trials. Sandborn *et al*[14] included patients who previously received TNF antagonist therapy; however, these patients were excluded from the other four trials. Despite these limitations, we believe that our analysis could contribute to the comprehensive evaluation of integrin antagonists in CD.

Our meta-analysis suggested that integrin antagonists were effective in improving CD response and remission rates with a similar rate of adverse reactions compared to placebo. However, due to the small size of samples in our study, large multicenter RCTs are needed to confirm our findings.

COMMENTS

Background

Crohn's disease (CD) can affect the gastrointestinal tract, with extraintestinal manifestations, and often leads to abdominal pain, fever, malaise, fatigue, diarrhea and bowel obstruction. Traditional therapies for CD are aminosalicylates, steroids, immunosuppressants and monoclonal antibodies. However, they all have an apparent adverse effects. Integrin antagonists including natalizumab and vedolizumab aim to block the interaction between leukocytes and endothelial cells. Previous studies have reported that integrin antagonists can inhibit inflammation.

Research frontiers

Natalizumab is a monoclonal antibody antagonizing $\alpha4\beta1$ and $\alpha4\beta7$ integrin-mediated interactions in the gut and brain, while vedolizumab is a humanized IgG1 monoclonal antibody for $\alpha4\beta7$ integrin. Current studies have reported that integrin antagonists can relieve symptoms in CD.

Innovations and breakthroughs

Previous studies have reported that natalizumab and vedolizumab are effective in CD treatment. However, these trials were small and there is still a lack of large multicenter trials. To evaluate the efficacy and safety of integrin antagonists, including natalizumab and vedolizumab, the authors performed a meta-analysis that overcame the limitation of small trials. To date, no meta-analysis has been published for CD that has evaluated the efficacy and safety of integrin antagonists. Thus, the aim of this study was to carry out a systematic literature review and meta-analysis of published RCTs in order to evaluate the efficacy and safety of the integrin antagonists, and this may contribute important results to the evidence-based health care evaluation of CD that might support clinical as well as financial decision making.

Applications

This study suggests that integrin antagonists are effective in improving CD response and remission rate although the treatment strategies are varied. Compared with placebo, integrin antagonists have a similar safety profile.

Terminology

CD is a relapsing systemic inflammatory disease that commonly affects the gastrointestinal tract with extraintestinal manifestations and associated immune disorders. CD often leads to abdominal pain, fever, malaise, fatigue, diarrhea, fistula formation, bowel obstruction, and malnutrition. Integrin antagonists are antibodies that aim to block the interaction between leukocytes and endothelial cells to inhibit inflammation including natalizumab and vedolizumab.

Peer-review

This study shows a meta-analysis that reviews the clinical evidence about the use of Integrin antagonists as a new treatment in refractory CD. Five papers meet with rigorous inclusion criteria and their analysis reported interesting data.

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