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**Integrin antagonists are effective and safe for Crohn’s disease treatment: a meta-analysis**

Ge WS *et al*. meta-analysis of integrin antagonists in CD

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**Abstract**

**Aim:** To evaluate the efficacy and safety of integrin antagonists including natalizumab and vedolizumab in Crohn’s disease.

**Methods:** Literatures were searched in Pubmed, Medline, Embase and the Cochrane library to screen citations from January 1990 to August 2014 in this study. Data analyses were done by using the Review Manager Software 5.2.

**Results:** A total of 1340 patients from 5 studies have been involved in this meta-analysis. During 6-12 wk treatment, integrin antagonists can increase 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 reaction (OR = 1.07, 95%CI: 0.83-1.38) and serious adverse reaction (OR = 0.81, 95%CI: 0.57-1.15).

**Conclusion:** The results have proven the efficacy and safety of integrin antagonists for Crohn disease treatment, though the treatment strategies were various.

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**Key words:** Crohn’s disease; Efficacy; Integrin antagonist; Meta-analysis; Safety

**Core tip:** α-integrin antagonists were used to treat Crohn’s disease, but their efficacy and safety are not certain yet. We performed this systematic review and meta-analysis to evaluate the efficacy and safety of integrin antagonists including natalizumab and vedolizumab in Crohn’s disease. During 6-12 wk treatment, integrin antagonists can increase the rate of clinical response and remission. And no significant difference was found between integrin antagonists and placebo treatments regarding their adverse reaction and serious adverse reaction. These results have proven the efficacy and safety of integrin antagonists for Crohn’s disease 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, fistulae 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 short term and bone loss, increased ocular pressure and diabetes in long term[5]. Immunosuppressants are used to suppress immune system and 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 α (TNF-α) inhibitors and α-integrin antagonists.

Natalizumab and Vedolizumab are the intergrin antagonists approved by the Food and Drug Administration. Natalizumab is a monoclonal antibody antagonizing α4β1 and α4β7 intergrin-mediated interactions in gut and brain[7]. It is effective in treating CD while limited by increasing the risk of progressive multifocal leukoencephalopathy (PML)[8]. Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody for α4β7 integrin. Since it only regulates gut lymphocyte trafficking, vedolizumab is not likely to cause PML[9].

Previous studies have indicated the efficacy of intergrin 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 intergrin antagonists for CD treatment.

**MATERIALS AND METHODS**

***Search strategy and inclusion criteria***

Databases (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) the studies were randomized controlled trials; and (2) the studies provided the data at least with one of the main outcomes, including rate of clinical response, rate of clinical remission, common adverse reaction and serious adverse reaction. Clinical remission was defined as Crohn’s Disease Activity Index (CDAI) score < 150 and clinical response was defined as a decrement of ≥ 70-point in CDAI score from baseline (Week 0).

***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; the number of common adverse reaction; the number of serious adverse reaction. The Jadad score was used to assess the quality of included studies. The studies with score no less than 3 were regarded as high quality RCTs, while studies with score less than 3 were defined as low quality RCTs.

***Statistical analysis***

Data analysis was performed by using the RevMan5.2 for each individual study, dichotomous data were reported as odds ratio (OR) with 95%CI. Heterogeneity between studies was assessed by Cochrane Q statistics and *I*2 test. A significant level of no less than 50% for *I*2 test was considered as evidence of heterogeneity. Fix effect model was used when there was no evidence of heterogeneity, otherwise random effect model was chosen. Ghosh *et al*[10] used 3 different treatment strategies and Feagan *et al*[11] used two treatment strategies. 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; five met the inclusion criteria for this study (Figure 1). A total of 1340 patients have been involved, in which 462 subjects were treated with natalizumab, 347 subjects were treated with vedolizumab and 531 subjects were treated with placebo. The information in these citations was summarized in Table 1. All five studies have been assessed by Jadad score system with score no less than 3 (Table 1).

***Clinical response***

Clinical response was reported in four studies. According to the results of the meta-analysis, integrin antagonists could increase 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***

Both Natalizumab and Vedolizumab were well tolerated during the treatment. They had similar rates of common adverse reaction (OR = 1.07, 95%CI: 0.83-1.38) and serious adverse reaction (OR = 0.81, 95%CI: 0.57-1.15) compared to placebo with no significant difference (Figures 4 and 5).

**Discussion**

The incidence of Crohn disease is increasing worldwide with more and more young patients and it requires life-long medical and surgical input[15]. Over the past decades, TNF-α inhibitors such as infliximab, adalimumab, 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 response to them at a rate of 10%-13% per year[17]. This led to researches looking for an alternative way to treat CD. It was found that the migration of leukocytes and other inflammatory cells into intestinal vasculature and the 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]. A RCT showed that vedolizumab can lead to clinical remission at 10 wk in TNF antagonist–failure patients[20].

Our meta-analysis suggested that short term treatment with intergin 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 week 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 not 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 reaction with placebo group. Previous studies showed that natalizumab could increase the risk of PML at a rate of 0.09 to 11 per 1000 patients[8]. Vedolizumab was designed to target the α4β7 integrin heterodimer and can not cross the blood–brain barrier[21]. There has been no reported case 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 reaction.

In addition, there were some limitations in our study. The treatment strategies were different in 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 was also various. Moreover, the inclusion criteria for patient were different in these trials. Sandborn *et al*[14] included patients who previously received TNF antagonist therapy; however these patients were excluded in the other four trials. Despite these limitations, we believed 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 reaction compared to placebo in the proper treatment strategy. However, due to the small size of samples in our study, large multicenter RCTs are needed to indentify 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 side effect. Intergrin antagonists including natalizumab and vedolizumab aim to block the interaction between leukocytes and endothelial cells. Previous studies have reported that intergrin antagonists can inhibit inflammation.

***Research frontiers***

Natalizumab is a monoclonal antibody antagonizing α4β1 and α4β7 intergrin-mediated interactions in gut and brain, while vedolizumab is a humanized immunoglobulin G1 monoclonal antibody for α4β7 intergrin. Current studies have reported intergrin antagonists can relieve symptoms in CD.

***Innovations and breakthroughs***

Previous studies have reported that natalizumab and vedolizumab are effective in CD treatment. However, the sample of these trials is small and there is still lack of large multicenter trials. To evaluate the efficacy and safety of intergrin antagonists including natalizumab and vedolizumab, the authors performed a meta-analysis which can overcome the limitation of single small sample trials. To date, no meta-analysis has been published yet in CD, which evaluates the efficacy and safety of the intergrin 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 intergrin antagonists, and this may contribute with important results to the evidence-based health care evaluation of CD that might support clinical as well as financial decision making.

***Applications***

Our study suggests that intergrin antagonists are effective in improving CD response and remission rate though the treatment strategies are various. Compared with placebo, intergrin antagonists have a similar safty.

***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, fistulae formation, bowel obstruction, and malnutrition. Intergrin antagonists are antibodies which 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. Nevertheless, it`s not clear, in the methods and discussion section, if these clinical trials are directed to treat only anti-TNF refractory patients. To be exact, the analysis must be clarifying the inclusion criteria of the analyzed clinical trials (five papers) in order to get good conclusion. The other hand, author recognized that the treatment strategies were different in each study, and these weaknesses must be remarked in the conclusion and, of course, in the abstract.

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**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 3mg/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 6mg/kg intravenous infusion at 0, 4 wk *n =* 51 | 35 | 7.8 | 298 | 5 |
| Natalizumab 3mg/kg intravenous infusion at 0, 4 wk *n =* 66 | 36 | 8.1 | 300 |
| Natalizumab 3mg/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 300mg intravenous infusion at 0, 4, 8 wk *n =* 259 | 38 | 10.1 | 304 | 5 |
| Placebo intravenous infusion at 0, 4, 8wk *n =* 250 | 38 | 10 | 300 |
| Feagan *et al*[11], 2008 | 8 | Vedolizumab 2mg/kg intravenous infusion at 0, 4 wk *n =* 65 | 39 | 8 | 297 | 5 |
| Vedolizumab 0.5mg/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 300mg 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.

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**Figure 1 Flow diagram of the studies identified.**



**Figure 2 Forest plots of clinical response.** Clinical response was defined as a decrement of ≥ 70-point in CDAI score from baseline (Week 0). Ghosh20031: 6 mg/kg natalizumab at 0, 4 wk; Ghosh 20032: 3 mg/kg natalizumab at 0, 4 wk; Ghosh 20033: 3 mg/kg natalizumab at 0 wk. Feagan 20081: 2 mg/kg vedolizumab at 0, 4 wk; Feagan 20082: 0.5 mg/kg vedolizumab at 0, 4 wk.



**Figure 3 Forest plots of clinical remission.** Clinical remission was defined as CDAI score < 150. Ghosh 20031: 6 mg/kg natalizumab at 0, 4 wk; Ghosh 20032: 3 mg/kg natalizumab at 0, 4 wk; Ghosh 20033: 3 mg/kg natalizumab at 0 wk. Feagan 20081: 2 mg/kg vedolizumab at 0, 4 wk; Feagan 20082: 0.5 mg/kg vedolizumab at 0, 4 wk.



**Figure 4 Forest plots of common adverse reaction.** Ghosh 20031: 6 mg/kg natalizumab at 0, 4 wk; Ghosh 20032: 3 mg/kg natalizumab at 0, 4 wk; Ghosh 20033: 3 mg/kg natalizumab at 0 wk. Feagan 20081: 2 mg/kg vedolizumab at 0, 4 wk; Feagan 20082: 0.5 mg/kg vedolizumab at 0, 4 wk.



**Figure 5 Forest plots of serious adverse reaction.** Ghosh 20031: 6mg/kg natalizumab at 0, 4 wk; Ghosh 20032: 3 mg/kg natalizumab at 0, 4 wk; Ghosh 20033: 3 mg/kg natalizumab at 0 wk. Feagan 20081: 2 mg/kg vedolizumab at 0, 4 wk; Feagan 20082: 0.5 mg/kg vedolizumab at 0, 4 wk.