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[Intervention Review]

Etrolizumab for induction of remission in ulcerative colitis

Greg Rosenfeld¹, Claire E Parker², John K MacDonald², Brian Bressler¹

¹Division of Gastroenterology, University of British Columbia, Vancouver, Canada. ²Robarts Clinical Trials, Robarts Research Institute, London, Canada

Contact: Brian Bressler, Division of Gastroenterology, University of British Columbia, 770-1190 Hornby Street, Vancouver, BC, V6Z 2K5, Canada. brian_bressler@hotmail.com.

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ABSTRACT

Background

Etrolizumab (rhuMAb beta7) is an anti-integrin that selectively targets the $\beta 7$ subunits of the $\alpha 4\beta 7$ and $\alpha E\beta 7$ integrins, which are involved in the pathogenesis of ulcerative colitis.

Objectives

The objectives of this review were to assess the efficacy and safety of etrolizumab for induction of remission in ulcerative colitis.

Search methods

We searched PubMed, MEDLINE, EMBASE, and the Cochrane Library (CENTRAL) from inception to 12 March 2015. References and conference abstracts were searched to identify additional studies.

Selection criteria

Randomized controlled trials (RCTs) trials in which etrolizumab was compared to placebo or another active comparator in patients with active ulcerative colitis were included.

Data collection and analysis

Two authors independently screened studies for inclusion, assessed methodological quality and extracted data. We assessed methodological quality using the Cochrane risk of bias tool. The primary outcome was failure to induce clinical remission (as defined by the primary studies). Secondary outcomes included failure to induce clinical improvement (as defined by the primary studies), failure to induce endoscopic remission (as defined by the primary studies), adverse events, serious adverse events, withdrawal due to adverse events, and health-related quality of life (as defined by the primary studies). We assessed the overall quality of the evidence using the GRADE criteria. We calculated the risk ratio (RR) and corresponding 95% confidence interval (CI) for each dichotomous outcome.

Main results

Two RCTs including 172 patients with moderate to severe UC who failed conventional therapy met the inclusion criteria. Both studies were rated as low risk of bias. We did not pool efficacy data from the two included studies due to differences in dose and route of administration. The small phase I study found no statistically significant differences between etrolizumab and placebo in the proportion of patients who failed to enter remission (RR 1.04, 95% CI 1.04 to 1.69; participants = 23) or respond at week 10 (RR 1.67, 95% CI 0.26 to 10.82; participants = 23). The phase II study reported on failure to enter clinical remission at weeks 6 and 10. In the etrolizumab group 91% (71/78) of patients failed to enter remission at week 6 compared to 95% (39/41) of placebo patients (RR 0.96, 95% CI 0.87 to 1.06). Subgroup analysis revealed no statistically significant differences by dose. At week 10, there was a statistically significant difference in clinical remission rates favouring etrolizumab over placebo. Of the patients who received etrolizumab, 85% (66/78) failed to enter remission at week 10 compared to 100%

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(41/41) patients in the placebo group (RR 0.86, 95% CI 0.77 to 0.95). A subgroup analysis by dose found a statistically significant difference in clinical remission rates favoring 100 mg etrolizumab over placebo (RR 0.81 CI 95% 0.68 to 0.96), but not 300 mg etrolizumab over placebo (RR 0.91, 95% CI 0.80 to 1.03). No significant heterogeneity was detected for this comparison ($P = 0.28$, $I^2 = 13.5\%$). GRADE analyses indicated that the overall quality of evidence for the clinical remission outcomes was moderate due to sparse data. Both of the included studies reported on safety. The outcome adverse events was initially pooled, however this analysis was removed due to high heterogeneity ($I^2 = 88\%$). The phase I study found no statistically significant difference between etrolizumab and placebo in the proportion of patients who had at least one adverse event. Ninety-five per cent (36/38) of etrolizumab patients had at least one adverse event compared to 100% (10/10) of placebo patients (RR 0.98, 95% CI 0.84 to 1.14). Common adverse events reported in the phase I study included exacerbation of UC, headache, fatigue, abdominal pain, dizziness, nasopharyngitis, nausea, arthralgia and urinary tract infection. There was a statistically significant difference between etrolizumab and placebo in the proportion of patients who had at least one adverse event. Fifty-six per cent (44/78) of etrolizumab patients had at least one adverse event compared to 79% of placebo patients (RR 0.71, 95% CI 0.55 to 0.91). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due to sparse data. Common adverse events reported in the phase II study included worsening UC, nasopharyngitis, nervous system disorders, headache and arthralgia. A pooled analysis of two studies indicates that there was no statistically significant difference in the proportion of patients who had a serious adverse event. Twelve per cent (14/116) of etrolizumab patients had a serious adverse event compared to 12% of placebo patients (6/49) (RR 0.92, 95% CI 0.36 to 2.34). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to very sparse data (20 events). Common serious adverse events included worsening of UC, impaired wound healing and bacterial peritonitis.

Authors' conclusions

Moderate quality evidence suggests that etrolizumab may be an effective induction therapy for some patients with moderate to severe ulcerative colitis who have failed conventional therapy. Due to small numbers of patients in dose subgroups the optimal dosage of etrolizumab is unclear. Due to sparse data we are uncertain regarding the risk of adverse events and serious adverse events. Further studies are needed to determine the efficacy and safety of etrolizumab in this patient population. There are five ongoing phase III etrolizumab trials and two ongoing open-label extension studies that will provide important new information on the efficacy, safety and optimal dose of this drug for the treatment of UC.

PLAIN LANGUAGE SUMMARY

Etrolizumab for the treatment of active ulcerative colitis

What is ulcerative colitis?

Ulcerative colitis is a long-term (chronic) inflammatory bowel disease. Symptoms include pain (abdominal cramping), a frequent need to defecate (fecal urgency) and bloody diarrhoea. When people with ulcerative colitis are experiencing symptoms the disease is said to be "active" and when symptoms stop this is called "remission".

What is etrolizumab?

Etrolizumab is a biologic medication. This medication is either injected under the skin with a syringe or infused into a vein (intravenous). Biologics suppress the immune system and lessen the inflammation associated with ulcerative colitis.

What did the researchers investigate?

The researchers investigated whether etrolizumab can stop symptoms of ulcerative colitis in people with active disease, and whether this medication causes harm (side effects). The researchers searched the medical literature up to March 12, 2015.

What did the researchers find?

The researchers identified two studies that included a total of 172 participants with moderate to severe ulcerative colitis who have failed treatment with immunosuppressives (e.g. steroids) or another biologic drug. Both studies compared etrolizumab to placebo (a fake medicine). Both studies were of high quality. The smaller study (48 participants) found no difference in remission rates between etrolizumab and placebo at week 10. The larger study (124 participants) found no difference between etrolizumab and placebo in the proportion of participants who achieved remission at week 6. However, there was a statistically meaningful difference in remission rates at week 10 favoring etrolizumab over placebo. In the larger study (124 participants) placebo participants were significantly more likely to have at least one side effect compared to those who took etrolizumab. Common side effects in this study included worsening ulcerative colitis, nasopharyngitis (common cold), nervous system disorders, headache and arthralgia (joint pain). In the other study (48 participants) there was no difference in the side effect rates between the placebo and etrolizumab groups. Common side effects in this study included worsening of ulcerative colitis, headache, fatigue (tiredness), abdominal pain, dizziness, nasopharyngitis (common cold), nausea, arthralgia (joint pain) and urinary tract infection. There was no meaningful difference between etrolizumab and placebo in the proportion of patients who experienced serious side effects. Serious side effects included worsening of ulcerative colitis and infection.

Etrolizumab may be better than placebo for producing remission in people with moderate to severe ulcerative colitis who have failed other treatments. Different doses of etrolizumab were investigated but it is unclear what dose is most effective. More studies are required to determine the effectiveness and safety of etrolizumab in patients with moderate to severe ulcerative colitis. Currently there are seven ongoing studies investigating etrolizumab treatment for ulcerative colitis. These studies will provide important new information on the effectiveness, safety and ideal dose of etrolizumab for the treatment of people with moderate to severe ulcerative colitis.