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Natalizumab for induction of remission in Crohn's disease (Review)

Nelson SML, Nguyen TM, McDonald JWD, MacDonald JK

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[Intervention Review]

Natalizumab for induction of remission in Crohn's disease

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ABSTRACT

Background

This systematic review update summarizes the current evidence on the use of natalizumab for induction of remission in Crohn's disease (CD).

Objectives

To determine the efficacy and safety of natalizumab for induction of remission in CD.

Search methods

We searched MEDLINE, Embase, CENTRAL, the Cochrane IBD Group Specialized Trials Register, and clinicaltrials.gov from inception to 10 May 2018.

Selection criteria

We included randomized controlled trials (RCTs) comparing natalizumab to a placebo or control therapy for induction of remission in CD.

Data collection and analysis

Two authors independently screened studies, extracted data and assessed methodological quality using the Cochrane risk of bias tool. The primary outcome was failure to enter clinical remission. Secondary outcomes included clinical response, mean change in Crohn's Disease Activity Index (CDAI), adverse events (AEs), withdrawal due to AEs and serious AEs. For dichotomous outcomes, we calculated the risk ratio (RR) and 95% confidence interval (95% CI). For continuous outcomes we calculated the mean difference (MD) and 95% CI. Data were pooled for meta-analysis when the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). We used GRADE to assess the overall quality of the evidence.

Main results

A total of five RCTs (1771 participants) were included. Four studies (1692 participants) compared one, two or three infusions of natalizumab (300 mg or 3 mg/kg or 6mg/kg) to placebo. One study (79 participants) compared three infusions of natalizumab (300 mg) and infliximab (5 mg/kg) to infliximab and placebo. Four studies were rated as low risk of bias. One study was rated as unclear risk of bias for selective reporting.

One, two and three infusions of natalizumab were superior to placebo for induction of remission and clinical response. Infusions were administered at weeks zero, four and eight. After one infusion, 76% (849/1117) of natalizumab participants failed to enter remission at 4 weeks compared to 83% (411/494) of placebo participants (RR 0.91, 95% CI 0.86 to 0.96, 3 studies, GRADE high quality). At 4 weeks, the RR for clinical response was 0.78 (95% CI 0.66 to 0.92, 3 studies, 1611 participants, GRADE moderate quality). After two infusions, after 8 weeks, 66% (693/1049) of natalizumab participants failed to enter remission compared to 77% (382/494) of placebo participants (RR 0.85, 95%

CI 0.76 to 0.95; 3 studies, GRADE moderate quality). At 8 weeks, the RR for clinical response was 0.73 (95% CI 0.58 to 0.91, 3 studies, 1543 participants, GRADE low quality). After three infusions, at 12 weeks, 61% (596/983) of natalizumab participants failed to enter remission compared to 73% (313/431) of placebo participants (RR 0.85, 95% CI 0.78 to 0.92, 2 studies, GRADE high quality). At 12 weeks, the RR for clinical response was 0.76 (95% CI 0.67 to 0.86, 2 studies, 1414 participants, GRADE high quality). One study (507 participants) reported on change in CADI from baseline. Natalizumab participants had a larger drop in mean CDAI scores than placebo participants at 4, 8 and 12 weeks.

The rates of AEs, withdrawals due to AEs and serious AEs were similar across groups at 4, 8 and 12 weeks. After one infusion, 74% (50/68) of natalizumab participants experienced an AE compared to 81% (51/63) of placebo participants (RR 0.91, 95% CI 0.75 to 1.09, GRADE moderate quality). Withdrawal due to an AE occurred in 1% (1/68) of natalizumab participants and 3% of placebo participants (RR 0.46, 95% CI 0.04 to 4.98, GRADE low quality). SAEs occurred in 10% (7/68) of natalizumab participants compared to 11% (7/63) of placebo participants (RR 0.93, 95% CI 0.34 to 2.49, GRADE low quality). After two infusions, 86% (57/66) of natalizumab participants experienced an AE compared to 81% (51/63) of placebo participants (RR 1.07, 95% CI 0.92 to 1.24, GRADE moderate quality). Withdrawal due to an AE occurred in 3% (2/66) natalizumab participants compared to 3% (2/63) placebo participants (RR 0.95, 95% CI 0.14 to 6.57, GRADE low quality). SAEs occurred in 9% (6/66) of natalizumab participants and 11% (7/63) of placebo participants (RR 0.82, 95% CI 0.29 to 2.30, GRADE low quality). After three infusions, 86% (848/984) of natalizumab participants experienced an AE compared to 83% (359/431) placebo participants (RR 1.03, 95% CI 0.98 to 1.08, GRADE high quality). Withdrawals due to AEs occurred in 8% (82/984) of natalizumab participants compared to 10% (45/431) of placebo participants (RR 0.86, 95% CI 0.59 to 1.26, GRADE moderate quality). SAEs occurred in 7% (65/983) of natalizumab participants and 8% (36/431) of placebo participants (RR 0.76. 95% CI 0.37 to 1.56, GRADE low quality). Adverse events included headache, nausea, nasopharyngitis, abdominal pain, fatigue, vomiting, and exacerbation of CD.

The study comparing combination therapy with natalizumab and infliximab to infliximab and placebo demonstrated similar remission rates at 10 weeks. Sixty-four per cent (33/52) of participants assigned to natalizumab and infliximab failed to achieve remission compared to 70% (19/27) assigned to placebo and infliximab (RR 0.90, 95% CI 0.65 to 1.24, GRADE moderate quality). The rates of AEs (moderate quality evidence), withdrawals due to AEs (low quality evidence) and serious AEs (low quality evidence) were similar across groups at 10 weeks. Adverse events included headache, exacerbation of CD, nausea, and nasopharyngitis.

Natalizumab is associated with the development of progressive multifocal leukoencephalopathy (PML) resulting in some patient deaths. There are currently no tests which can reliably predict those at risk of developing PML.

Authors' conclusions

High quality data suggest that natalizumab is effective for induction of clinical remission and response in some patients with moderately to severely active CD. However, none of the included studies had the power to detect rare but serious adverse events such as PML. Due to the association with PML, and the availability of alternative agents that are not associated with PML, natalizumab is not likely to be used in patients who fail currently available medical therapy. The use of natalizumab in select patients (e.g. patients allergic to different biologics) needs to be carefully considered against the potential risk of developing PML. Futher studies of natalizumab are not likely to be done.

PLAIN LANGUAGE SUMMARY

Natalizumab for treatment of active Crohn's disease

Background

Crohn's disease (CD) is a chronic inflammatory disease of the intestines. CD frequently occurs in the lower part of the small intestine, called the ileum, but it can affect any part of the digestive tract. Common symptoms include abdominal pain, often in the lower right area, and diarrhea. When people with CD are experiencing symptoms, the disease is called 'active'. When the symptoms stop, it is called 'remission'. Natalizumab and infliximab are biologic medications. These medications are directly infused into a vein (intravenous). Biologics suppress the immune system and reduce the inflammation associated with CD. Biologics are often given to people with moderate to severe CD who are unable to achieve remission despite treatment with standard drugs.

Study characteristics

We performed a comprehensive literature review and identified five randomized controlled trials (an experiment in which participants are randomly assigned to receive two or more interventions and the results are compared) that involved a total of 1771 participants. Four studies (1692 participants) compared one, two or three intravenous infusions of natalizumab (300 mg or 3 mg/kg or 6mg/kg) to placebo (a sham infusion - an infusion that was identical in appearance to natalizumab but did not contain any active medicine). These studies followed participants for 12 weeks. One study (79 participants) compared three intravenous infusions of natalizumab (300 mg) and infliximab (5 mg/kg) to infliximab and placebo. The participants in this study were unable to achieve remission despite treatment with the biologic drug infliximab. This study followed participants for 10 weeks. All of the studies were high quality.

Key results

Depending upon the study, intravenous infusions of natalizumab or placebo were administered at weeks zero, four and eight. One, two and three infusions of natalizumab were superior to placebo for induction of remission and clinical response (improvement in symptoms of active CD). The rates of side effects, study withdrawals due to side effects and serious side effects were similar across the natalizumab and placebo groups at 4, 8 and 12 weeks. Common side effects included headache, nausea, nasopharyngitis (common cold), abdominal pain, fatigue, vomiting and worsening of Crohn's disease.

The study comparing combination therapy with natalizumab and infliximab to infliximab and placebo demonstrated similar remission rates at 10 weeks. The rates of side effects, withdrawals due to side effects and serious side effects were similar across groups at 10 weeks. Common adverse events included headache, worsening of Crohn's disease, nausea, and nasopharyngitis.

The included trials were not designed to detect serious side effects that occur infrequently. Natalizumab is associated with the development of progressive multifocal leukoencephalopathy (PML) resulting in some patient deaths. PML is a serious infection of the nervous system that can often be fatal. There are currently no tests which can reliably predict those at risk of developing PML.

Quality of evidence

Overall, the quality of evidence for each outcome was generally high.

Conclusions

High quality data suggest that natalizumab is effective for induction of clinical remission and response in some patients with moderately to severely active Crohn's disease. Due to the association with PML, and the availability of alternative agents that are not associated with PML, natalizumab is not likely to be used in patients who fail currently available medical therapy for Crohn's disease. The use of natalizumab in select patients (e.g. people allergic to different biologics) needs to be carefully considered against the potential risk of developing PML. Futher studies of natalizumab are not likely to be done.

Summary of findings for the main comparison. One infusion of natalizumab (300 mg or 3 mg/kg) compared to placebo for induction of remission in Crohn's disease

One infusion of natalizumab (300 mg or 3 mg/kg) compared to placebo for induction of remission in Crohn's disease

Patient or population: Participants with active Crohn's disease
Setting: Outpatient
Intervention: One infusion of natalizumab (300 mg or 3 mg/kg)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with one infusion of natalizumab (300 mg or 3 to 4 mg/kg)				
Failure to induce remission at 2 weeks	902 per 1,000	848 per 1,000 (803 to 884)	RR 0.94 (0.89 to 0.98)	1132 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Failure to induce remission at 4 weeks	832 per 1,000	757 per 1,000 (716 to 799)	RR 0.91 (0.86 to 0.96)	1611 (3 RCTs)	⊕⊕⊕⊕ HIGH	
Failure to induce clinical response at 2 weeks	680 per 1,000	558 per 1,000 (449 to 687)	RR 0.82 (0.66 to 1.01)	1102 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
Failure to induce clinical response at 4 weeks	613 per 1,000	478 per 1,000 (405 to 564)	RR 0.78 (0.66 to 0.92)	1611 (3 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
Adverse events up to week 12	810 per 1,000	737 per 1,000 (607 to 882)	RR 0.91 (0.75 to 1.09)	131 (1 RCT)	⊕⊕⊕⊖ MODERATE[3]	
Withdrawal due to adverse events up to week 12	32 per 1,000	15 per 1,000 (1 to 158)	RR 0.46 (0.04 to 4.98)	131 (1 RCT)	⊕⊕⊖⊖ LOW [4]	
Serious adverse events up to week 12	111 per 1,000	103 per 1,000 (38 to 277)	RR 0.93 (0.34 to 2.49)	131 (1 RCT)	⊕⊕⊖⊖ LOW [5]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious inconsistency (I^2=40%)
[2] Downgradded one level due to serious inconsistency (I^2= 63%)
[3] Downgraded two levels due to serious imprecision (101 events)
[4] Downgraded two levels due to very serious imprecision (3 events)
[5] Downgraded two levels due to very serious imprecision (14 events)

Summary of findings 2. Two infusions of natalizumab (300 mg or 3 mg/kg) compared to placebo for induction of remission in Crohn's disease

Two infusions of natalizumab (300 mg or 3 mg/kg) compared to placebo for induction of remission in Crohn's disease

Patient or population: Participants with active Crohn's disease
Setting: Outpatient
Intervention: Two infusions of natalizumab (300 mg or 3 mg/kg)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with two infusions of natalizumab (3 to 4 mg/kg)				
Failure to induce remission at 6 weeks	762 per 1,000	648 per 1,000 (595 to 709)	RR 0.85 (0.78 to 0.93)	1034 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Failure to induce remission at 8 weeks	773 per 1,000	657 per 1,000 (588 to 735)	RR 0.85 (0.76 to 0.95)	1543 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Failure to induce clinical response at 6 weeks	512 per 1,000	338 per 1,000 (179 to 640)	RR 0.66 (0.35 to 1.25)	1034 (2 RCTs)	⊕⊕⊖⊖ LOW [2]	
Faliure to induce clinical response at 8 weeks	571 per 1,000	417 per 1,000 (331 to 519)	RR 0.73 (0.58 to 0.91)	1543 (3 RCTs)	⊕⊕⊖⊖ LOW [3]	
Adverse events up to week 12	810 per 1,000	866 per 1,000 (745 to 1,000)	RR 1.07 (0.92 to 1.24)	129 (1 RCT)	⊕⊕⊕⊖ MODERATE [4]	

Withdrawal due to adverse events up to week 12	32 per 1,000	30 per 1,000 (4 to 209)	RR 0.95 (0.14 to 6.57)	129 (1 RCT)	⊕⊕⊖⊖ LOW [5]
Serious adverse events up to week 12	111 per 1,000	91 per 1,000 (32 to 256)	RR 0.82 (0.29 to 2.30)	129 (1 RCT)	⊕⊕⊖⊖ LOW [6]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious inconsistency (I^2= 53%)
[2] Downgraded two levels due to very serious inconsistency (I^2= 87%)
[3] Downgraded two levels due to very serious inconsistency (I^2= 68%)
[4] Downgraded one level due to serious imprecision (108 events)
[5] Downgraded two levels due to very serious imprecision (4 events)
[6] Downgraded two levels due to very serious imprecision (13 events)

Summary of findings 3. Two infusions of natalizumab (6 mg/kg) compared to placebo for induction of remission in Crohn's disease

Two infusions of natalizumab (6 mg/kg) compared to placebo for induction of remission in Crohn's disease

Patient or population: Participants with active Crohn's disease
Setting: Outpatient
Intervention: Two infusions of natalizumab (6 mg/kg)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with two infusions of natalizumab (6 mg/kg)				
Failure to induce remission at 6 weeks	730 per 1,000	686 per 1,000 (540 to 869)	RR 0.94 (0.74 to 1.19)	114 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	

Failure to induce remission at 8 weeks	841 per 1,000	572 per 1,000 (437 to 740)	RR 0.68 (0.52 to 0.88)	114 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]
Failure to induce clinical response at 6 weeks	619 per 1,000	433 per 1,000 (297 to 625)	RR 0.70 (0.48 to 1.01)	114 (1 RCT)	⊕⊕⊕⊖ MODERATE [3]
Failure to induce clinical response at 8 weeks	651 per 1,000	449 per 1,000 (319 to 644)	RR 0.69 (0.49 to 0.99)	114 (1 RCT)	⊕⊕⊕⊖ MODERATE [4]
Adverse events up to week 12	810 per 1,000	785 per 1,000 (648 to 947)	RR 0.97 (0.80 to 1.17)	114 (1 RCT)	⊕⊕⊕⊖ MODERATE [5]
Withdrawal due to adverse events up to week 12	32 per 1,000	59 per 1,000 (10 to 339)	RR 1.85 (0.32 to 10.67)	114 (1 RCT)	⊕⊕⊖⊖ LOW [6]
Serious adverse events up to week 12	111 per 1,000	118 per 1,000 (42 to 328)	RR 1.06 (0.38 to 2.95)	114 (1 RCT)	⊕⊕⊖⊖ LOW [7]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision (81 events)
[2] Downgraded one level due to serious imprecision (82 events)
[3] Downgraded one level due to serious imprecision (61 events)
[4] Downgraded one level due to serious imprecision (64 events)
[5] Downgraded one level due to serious imprecision (91 events)
[6] Downgraded two levels due to very serious imprecision (5 events)
[7] Downgraded two levels due to very serious imprecision (13 events)

Summary of findings 4. Three infusions of natalizumab (300 mg) compared to placebo for induction of remission in Crohn's disease

Three infusions of natalizumab (300 mg) compared to placebo for induction of remission in Crohn's disease

Patient or population: Participants with active Crohn's disease
Setting: Outpatient
Intervention: Three infusions of natalizumab (300 mg)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with three infusions of natalizumab (300 mg)				
Failure to induce remission at 10 weeks	696 per 1,000	633 per 1,000 (564 to 703)	RR 0.91 (0.81 to 1.01)	905 (1 RCT)	⊕⊕⊕⊕ HIGH	
Failure to induce remission at 12 weeks	726 per 1,000	617 per 1,000 (566 to 668)	RR 0.85 (0.78 to 0.92)	1414 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Failure to induce clinical response at 10 weeks	514 per 1,000	437 per 1,000 (370 to 514)	RR 0.85 (0.72 to 1.00)	905 (1 RCT)	⊕⊕⊕⊕ HIGH	
Failure to induce clinical response at 12 weeks	531 per 1,000	404 per 1,000 (356 to 457)	RR 0.76 (0.67 to 0.86)	1414 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Adverse events up to week 12	833 per 1,000	858 per 1,000 (816 to 900)	RR 1.03 (0.98 to 1.08)	1415 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Withdrawal due to adverse event up to week 12	104 per 1,000	90 per 1,000 (62 to 132)	RR 0.86 (0.59 to 1.26)	1415 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Serious adverse events up to week 12	84 per 1,000	63 per 1,000 (31 to 130)	RR 0.76 (0.37 to 1.56)	1414 (2 RCTs)	⊕⊕⊖⊖ LOW [2 3]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision (127 events)

[2] Downgraded one level due to serious imprecision (101 events)
[3] Downgraded one level due to serious inconsistency(I^2 = 62%)

Summary of findings 5. Three infusions of natalizumab (300 mg) and two infusions of infliximab (5 mg/kg) compared to placebo and two infusions of infliximab for induction of remission in Crohn's disease

Three infusions of natalizumab (300 mg) and two infusions of infliximab compared to placebo and two infusions of infliximab for induction of remission in Crohn's disease

Patient or population: Participants with active Crohn's disease despite current treatment with infliximab
Setting: Outpatient
Intervention: Three infusions of natalizumab (300 mg) and two infusions of infliximab
Comparison: Placebo and two infusions of infliximab

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo and two infusions of infliximab (5 mg/kg)	Risk with three infusions of natalizumab (300 mg) and two infusions of infliximab				
Failure to induce clinical remission at week 10	704 per 1,000	633 per 1,000 (457 to 873)	RR 0.90 (0.65 to 1.24)	79 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	
Failure to induce clinical response at 10 weeks	Not reported					This outcome was not reported
Adverse events up to week 10	1,000 per 1,000	930 per 1,000 (850 to 1,000)	RR 0.93 (0.85 to 1.03)	79 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]	
Withdrawal due to adverse events up to week 10	37 per 1,000	7 per 1,000 (0 to 155)	RR 0.18 (0.01 to 4.18)	79 (1 RCT)	⊕⊕⊖⊖ LOW [3]	
Serious adverse events up to week 10	37 per 1,000	19 per 1,000 (1 to 296)	RR 0.52 (0.03 to 7.98)	79 (1 RCT)	⊕⊕⊖⊖ LOW [4]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] Downgraded one level due to serious imprecision (52 events)
[2] Downgraded one level due to serious imprecision (75 events)
[3] Downgraded two levels due to very serious imprecision (1 event)
[4] Downgraded two levels due to very serious imprecision (2 events)

BACKGROUND

Description of the condition

Crohn's disease (CD) is a condition characterized by a chronic inflammation of the gastrointestinal tract. CD is associated with significant morbidity and decreased quality of life. The highest incidence and prevalence rates for CD have been reported in northern Europe, the United Kingdom and North America. However, CD rates are increasing in other areas of the world including Asia, Africa and Latin America (Loftus 2004). In North America, the incidence of CD ranges from 3.1 to 14.6 cases per 100,000 person years for Crohn's disease and prevalence ranges from 26 to 199 cases per 100,000 persons (Loftus 2004). Common symptoms of CD include diarrhea, abdominal pain, intestinal bleeding and weight loss (Lichtenstein 2009). A combination of tests are usually done to confirm a diagnosis of CD. These tests may include: blood work, colonoscopy, CT scan, MRI, capsule endoscopy and balloon-assisted enteroscopy.

The pathophysiology of CD is thought result from a combination of environmental and genetic factors. CD may be due to an immune response from an antigen presentation, with an increased response from the Th1 cells and cytokines such as IL-12 and tumor necrosis factor-alpha (TNF-α) (Thoreson 2007;Tsianos 2012). Current treatment for CD may include biologics, antiinflammatory drugs, and immunosuppressives. Patients who fail medical therapy or develop complications may require surgical intervention.

Description of the intervention

Natalizumab (Tysabri®, Elan Pharmaceuticals and Biogen Idec), a recombinant humanized IgG4 monoclonal antibody, is a member of a class of molecules known as selective adhesion molecule inhibitors (Biogen 2017). Natalizumab has been linked to the development of progressive multifocal leukoencephalopathy (PML) which is a rare and often fatal viral disease that causes inflammation of the white matter in the brain (Biogen 2017).

How the intervention might work

Natalizumab blocks adhesion and subsequent migration of leukocytes into the gut by binding the α4 integrin. The results of animal studies suggest that α4 integrin blockade could be a useful therapy for inflammatory bowel disease. Treatment with natalizumab resulted in reduced intestinal inflammation and improvement of symptoms of inflammatory bowel disease in a cotton-top tamarin model of colitis (Hesterberg 1996; Podolsky 1993). The results of five randomized controlled induction trials suggest that natalizumab may be an effective treatment for active Crohn's disease (Ghosh 2003; Gordon 2001; Sandborn 2005; Sands 2007; Targan 2007).

Why it is important to do this review

This systematic review summarizes the current evidence regarding the use of natalizumab for the induction of remission in Crohn's disease and updates previously published versions of this review (MacDonald 2006; MacDonald 2007).

OBJECTIVES

To determine the efficacy and safety of natalizumab for induction of remission in Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing natalizumab to a placebo or control therapy were considered for inclusion.

Types of participants

Participants include patients ≥ 18 years of age with Crohn's disease defined by conventional clinical, radiological and endoscopic criteria, which is categorized as being active (Crohn's disease activity index 'CDAI' >150).

Types of interventions

Interventions that involve natalizumab versus placebo or a control therapy were considered for inclusion.

Types of outcome measures

The primary outcome was the number of patients achieving remission as defined by the primary studies, and expressed as a percentage of the patients randomized (intention-to-treat analysis). Secondary outcomes included clinical response, mean CDAI, adverse events, serious adverse events (e.g. PML) and withdrawal because of adverse events.

Search methods for identification of studies

Electronic searches

We searched CENTRAL, the Cochrane IBD Group Specialized Register, MEDLINE, Embase and clinicaltrials.gov from inception to 10 May 2018. The search strategy is reported in Appendix 1. No language, publication status, or date limits were applied.

Searching other resources

In addition to the electronic searches, abstracts from major gastroenterological meetings were searched to identify research submitted in abstract form only. Previoiusly personal contacts and leaders in the field were contacted to identify other studies which may not be published. The manufacturer of natalizumab (Elan Pharmaceuticals Inc., San Diego, CA, USA and Biogen Idec, Inc., Cambridge, MA, USA) was contacted for additional data for the previous version of the review.

Data collection and analysis

Selection of studies

All publications identified by the search strategy were assessed using pre-specified eligibility criteria. Relevant studies were selected according to the eligibility criteria and were retrieved for full-text review and independently assessed by two authors (SMLN and TMN). Any disagreement among authors was resolved by consensus.

Data extraction and management

Two authors (SMLN and TMN) independently extracted data on patients, methods, interventions, and outcomes, using a data extraction form. Any disagreement among authors was resolved by consensus.

Assessment of risk of bias in included studies

Two authors (SMLN and TMN) independently assessed the risk of bias as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Factors assessed included:

1. sequence generation (i.e. was the allocation sequence adequately generated?);

2. allocation sequence concealment (i.e. was allocation adequately concealed?);

3. blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?);

4. incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);

5. selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?); and

6. other potential sources of bias (i.e. was the study apparently free of other problems that could put it at a high risk of bias?).

A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias. Any disagreement between authors was resolved by consensus. Study authors were contacted when insufficient information was provided to assess the risk of bias.

The quality of the evidence supporting the outcomes reported in this review was evaluated using the GRADE approach (Guyatt 2008; Schünemann 2011). Outcome data were rated as high, moderate, low or very low. Outcome data from randomized controlled trials begins as high quality but it can be downgraded based on a number of criteria. These criteria include risk of bias in the included studies, indirect evidence (by comparison, population, setting), inconsistency (unexplained heterogeneity), imprecise results (i.e. wide confidence intervals) and the likelihood of publication bias.

Measures of treatment effect

For dichotomous outcomes, we calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI). For continuous outcomes, we calculated the mean difference (MD) and 95% CI.

Unit of analysis issues

For multi-arm trials with a placebo group and multiple treatment dose groups, we split the placebo group in half to avoid a unit of analysis error. For cross-over studies, we only included the first part of the study to avoid potential carry over effects. When there were repeated observations on participants, we assessed outcomes at fixed time points as defined by the included studies. For outcomes where the events reoccurred (i.e. adverse events), we included the proportion of patients who experienced at least one event.

Dealing with missing data

For dichotomous outcomes, we analyzed data on an intention-to-treat basis. For studies with missing data with no explanation, the patient outcome was considered to be a treatment failure. For missing continuous outcomes, we conducted an available case analysis.

Assessment of heterogeneity

The presence of heterogeneity among studies was assessed using the Chi^2 and I^2 statistics. As the Chi^2 test has low power in the situation of a meta-analysis, when trials have small sample size or are few in number, a P value of 0.10 was regarded as statistically significant. An I^2 of 30% to 60% represents moderate heterogeneity, an I^2 of 50% to 90% represents substantial heterogeneity and an I^2 of 75% to 100% represents considerable heterogeneity. We investigated heterogeneity by visually assessing the forest plot to identify any outliers. If outliers were identified, a sensitivity analysis was conducted to explore possible explanations for the heterogeneity.

Assessment of reporting biases

We assessed reporting bias by comparing the pre-specified outcomes published in the protocols to the final outcomes reported in the manuscripts. If the protocol was not found, we would compare the pre-specified outcomes in the methods section of the manuscript to the results section. If there were more than 10 included studies in a pooled analysis, we planned to investigate publication bias by constructing funnel plots.

Data synthesis

Data from the included trials were combined for meta-analysis when the interventions, patients and outcomes were similar (determined by consensus). We calculated the pooled RR and 95% CI for dichotomous outcomes. For continuous outcomes, we calculated the pooled MD and corresponding 95% CI. For continuous outcomes that used different scales to measure the same outcome, the standardized mean difference (SMD) and corresponding 95% CI was calculated. A fixed-effect model was used for pooling data when statistical heterogeneity was not present. When statistical heterogeneity was present a random-effects model was used to pool data.

Subgroup analysis and investigation of heterogeneity

We did not pre-specify any subgroup analyses.

Sensitivity analysis

Sensitivity analyses were conducted to explore potential explanations for heterogeneity.

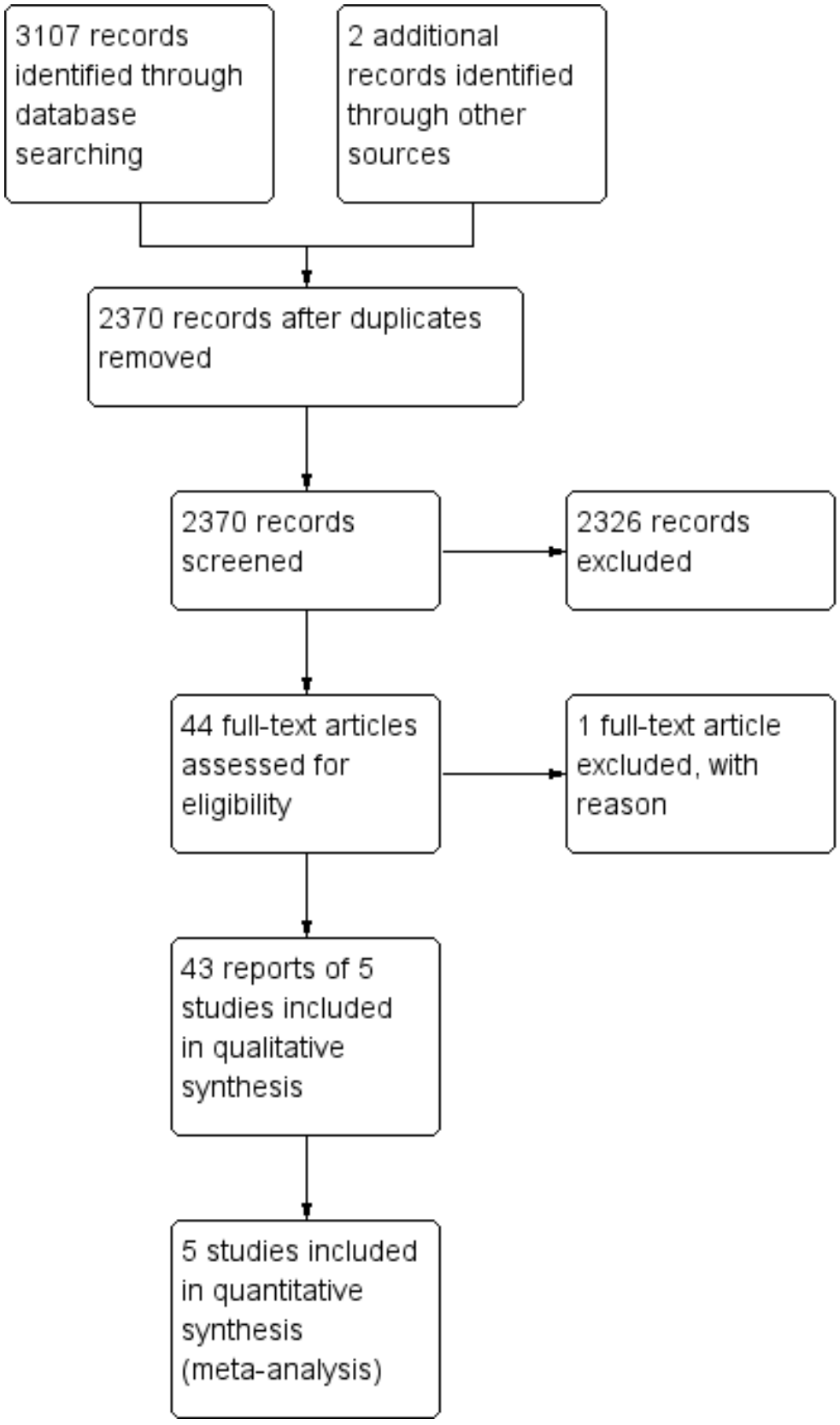
RESULTS

Description of studies

Results of the search

A literature search conducted on 10 May 2018 identified 3107 records. Two additional studies were identified through searching conference abstracts and other sources. After duplicates were removed, a total of 2370 records were left to review (Figure 1). Two authors (SMLN and TMN) independently reviewed the titles and abstracts of these records and 44 full text articles were selected for full text review. One study was excluded (Kane 2012). Forty-three reports of five randomized, double-blind, placebo-controlled trials (total of 1771 participants) met the pre-defined inclusion criteria and were included in the review (Ghosh 2003; Gordon 2001; Sandborn 2005; Sands 2007; Targan 2007).

Figure 1. Study flow diagram.



Included studies

Ghosh 2003

In this study, 248 adult patients (≥ 18 years) with clinical evidence of moderate to severe Crohn's disease, defined by a CDAI of at least 220 but no more than 450 were recruited from 35 centers in Belgium, the Czech Republic, Denmark, Germany, Israel, the Netherlands, Sweden and the United Kingdom for a twelve week induction trial. Patients who received methotrexate, cyclosporine, or any investigational drugs within three months prior to randomization were excluded. Patients taking azathioprine or 6-mercaptopurine were required to have a stable dose for at least four months prior to randomization. Other exclusion criteria included: prior treatment with any antibody agent, current use of more than 25 mg per day of oral prednisolone or another corticosteroid at an equivalent dose, elemental diet or parenteral nutrition, infectious or neoplastic diseases of the bowel, bowel surgery within three months prior to randomization, the presence of an ostomy, the presence of symptoms due mainly to fibrotic strictures, and a clinical impression that the patient would likely require abdominal surgery. Patients were randomized to one of four treatment groups using a computer-generated, site stratified, block randomization schedule. The patients and study personnel were not aware of treatment assignment. Each group received two intravenous infusions four weeks apart at week zero and week four. The four treatment groups consisted of two infusions of placebo (n = 63), one infusion of natalizumab (3 mg/kg) and one infusion of placebo (n = 68), two infusions of natalizumab (3 mg/kg; n = 66), and two infusions of natalizumab (6 mg/kg; n = 51). The primary outcome variable was the proportion of patients who entered remission at week six. Clinical remission was defined as a CDAI score of less than 150. Clinical response, a secondary outcome, was defined as a decrease in the CDAI score of at least 70 points from baseline. Other secondary outcome variables included the serum concentration of C-reactive protein (CRP), absolute neutrophil counts, serum antibodies against natalizumab and health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ). Patients were evaluated at baseline and weeks two, four, six, eight and twelve.

Gordon 2001

In this study, 30 adult patients (≥ 18 years of age) with clinical evidence of mild to moderately active Crohn's disease, defined by a CDAI of ≥ 151 and ≤ 450 were recruited from two centers in the United Kingdom. Patients had Crohn's disease confirmed by two or more of the following diagnostic criteria at least three months prior to study entry: history, radiologic or endoscopic intestinal appearance, histology, presence of Crohn's related fistula and abscess formation. Female patients had to use effective contraception throughout the study follow-up period. Oral corticosteroids (≤ 40 mg prednisolone or ≤ 9 mg budesonide per day) were allowed if the dose was stable within two weeks of study entry. Patients receiving 5-ASA drugs or azathioprine or 6-mercaptopurine were included if treatment had not been started within two months or the dose increased within four months of study entry. Exclusion criteria included: pregnancy or breast-feeding; patients weighing more than 100 kg; patients with a CDAI score > 450 or were inpatients because of Crohn's disease; patients treated with cyclosporine, methotrexate, or tacrolimus therapy; patients who had abdominal surgery within three months of entry or were considered likely to require surgery within three months of study entry; patients with an ileostomy or colostomy; patients with laboratory-confirmed intestinal infection; and patients with a current or past malignant neoplasm. Patients were randomized in a 2 to 1 ratio using a table of random numbers to receive an intravenous infusion of natalizumab (3 mg/kg; n = 18) or placebo (n = 12). The patients and study personnel were not aware of treatment assignment. The primary outcome variable was the change in mean CDAI at two weeks post infusion. Clinical remission was defined as a CDAI score of less than 150. Other secondary outcome variables included IBDQ, serum levels of CRP, erythrocyte sedimentation rate, full blood count, peripheral blood T cells and B cells, serum natalizumab and anti-natalizumab antibody concentrations. Patients were evaluated at study entry and at weeks one, two, four, eight, and twelve post infusion.

Sandborn 2005

In the ENACT-1 study, 905 adult patients (≥ 18 years of age) with Crohn's disease of at least 6 months duration who had moderately to severely active disease as defined by a baseline CDAI score of 220 to 450 points were recruited from 142 centers in North America, Europe and selected countries around the world for a twelve week induction trial. Radiologic or endoscopic studies were required within 36 months and after surgery for Crohn's disease to confirm the presence of active Crohn's disease. Concomitant medication for Crohn's disease, including stable doses of 5-ASA drugs, prednisone (≤ 25 mg/day), budesonide, azathioprine, 6-mercaptopurine, methotrexate, and antibiotics were permitted. Exclusion criteria included: patients with short bowel syndrome, an ostomy, a total colectomy, a stricture with obstructive symptoms, draining fistulas, abdominal abscess, previous natalizumab treatment or previous anti-tumour necrosis factor-alpha (TNF-α) therapy within three months prior to study entry. Enrolment of patients who were nonresponders to anti-TNF-α treatment was limited to a maximum of 30% of total study enrolment. Patients were screened for eligibility two weeks prior to entry. Patients were randomized in a 4 to 1 ratio to receive an infusion of either 300 mg of natalizumab (n = 724) or placebo (n = 181) for a total of three infusions given at weeks zero, four and eight. Randomization was performed centrally and prospectively stratified by disease activity (CDAI < 330 versus CDAI ≥ 330) and concurrent corticosteroid therapy. A pharmacist prepared each infusion of natalizumab or an identical appearing placebo. Neither the patients nor the study investigators were aware of treatment assignment. Patients were assessed at weeks two, four, six, eight, ten and twelve. The IBDQ was administered to assess quality of life at weeks zero, six and ten. The primary outcome variable was response at week ten which was defined as a reduction of ≥ 70 points in the CDAI score from baseline. Remission was defined as a CDAI score of less than 150. Other secondary outcome variables included serum levels of CRP and mean lymphocyte counts. At each assessment visit, adverse events and concomitant medications were recorded and samples were collected for laboratory evaluations. Safety evaluations included vital signs, physical examinations, hematology, serum biochemistry, and urinalysis. The Sandborn 2005 manuscript reports the results of both a natalizumab induction trial (ENACT-1) and a maintenance of remission trial (ENACT-2). The results of ENACT-2 were excluded because it was a maintenance of remission trial.

Sands 2007

In this study, 79 adult patients (≥ 18 years of age) with active Crohn's disease receiving infliximab but not in remission (CDAI > 150) were randomized. Patients were required to have at least

a 6-month clinical history of Crohn's disease and to have been on therapy with infliximab every 8 weeks at the time of the screening visit. Patients should have received an infusion 10 weeks before randomization and were infused again 2 weeks before randomization. Patients were permitted concurrent use of certain Crohn's disease medications during the study if they were receiving a stable dose before randomization. Permitted medications included oral 5-aminosalicylic acid (5-ASA) compounds, if on a stable dose for at least 4 weeks; oral antibiotics if on a stable dose for at least 4 weeks; oral corticosteroids not exceeding 25 mg prednisolone or its equivalent for at least 4 weeks and a stable dose for at least 2 weeks; and immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate) for at least 4 months before entry and at a stable dose for at least 8 weeks. For patients receiving allowed immunosuppressants, the dose could be decreased at the discretion of the investigator. Exclusion criteria included: concurrent use of herbal preparations, rectal steroids, rectal 5-ASAs, tacrolimus, cyclosporine, mycophenolate mofetil, any investigational or experimental agents, and prior natalizumab therapy, bowel surgery within the 3 months before week 0, persistent intestinal obstruction, bowel perforation, uncontrolled bleeding, abdominal abscess, infection, symptoms largely a result of fibrotic strictures, neoplastic disease of the bowel, a positive stool culture for enteric pathogens at screening, nasogastric or nasoenteric tube feeding, an elemental diet, total parenteral nutrition within 2 weeks of week 0, and abnormal liver function tests at screening. The primary outcome was to evaluate the safety and tolerability of combined natalizumab-infliximab therapy while remission and clinical response rates were evaluated as secondary outcomes. Other secondary outcomes included inflammatory marker assessment (e.g. serum CRP), pharmacokinetics, pharmacodynamics, and health-related quality of life.

Targan 2007

In the ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission) study, 509 adult patients (≥ 18 years of age) with moderately to severely active Crohn's disease and objective evidence of active inflammation indicated by elevated CRP levels were recruited from 114 centers in North America, Europe and selected countries around the world for a twelve week induction trial. Patients with a CDAI score between 220 and 450 and CRP levels greater than the upper limit of normal (2.87 mg/L) were randomized in a 1 to 1 ratio to receive an infusion of either 300 mg natalizumab (n = 259) or placebo (n = 250) for a total of three infusions given at weeks zero, four and eight. Efficacy and safety were assessed at weeks four, eight and twelve. The primary outcome variable was response by week eight which was defined as a reduction of ≥ 70 points in the CDAI score from baseline that sustained through week twelve. Secondary outcome variables included the proportion of patients achieving response at week twelve, a clinical remission (defined as a CDAI score of less than 150) by week eight sustained to week twelve, and the proportion of patients with remission at week 12. Tertiary outcomes included proportion achieving a ≥100-point CDAI score decrease at weeks eight and twelve, achieving clinical response or remission at weeks four and eight, response at week eight, time to clinical remission, mean change in baseline CDAI, platelets and CRP at weeks four, eight and twelve, and to evaluate the effects of natalizumab on quality of life (IBDQ and SF-36) at week twelve.

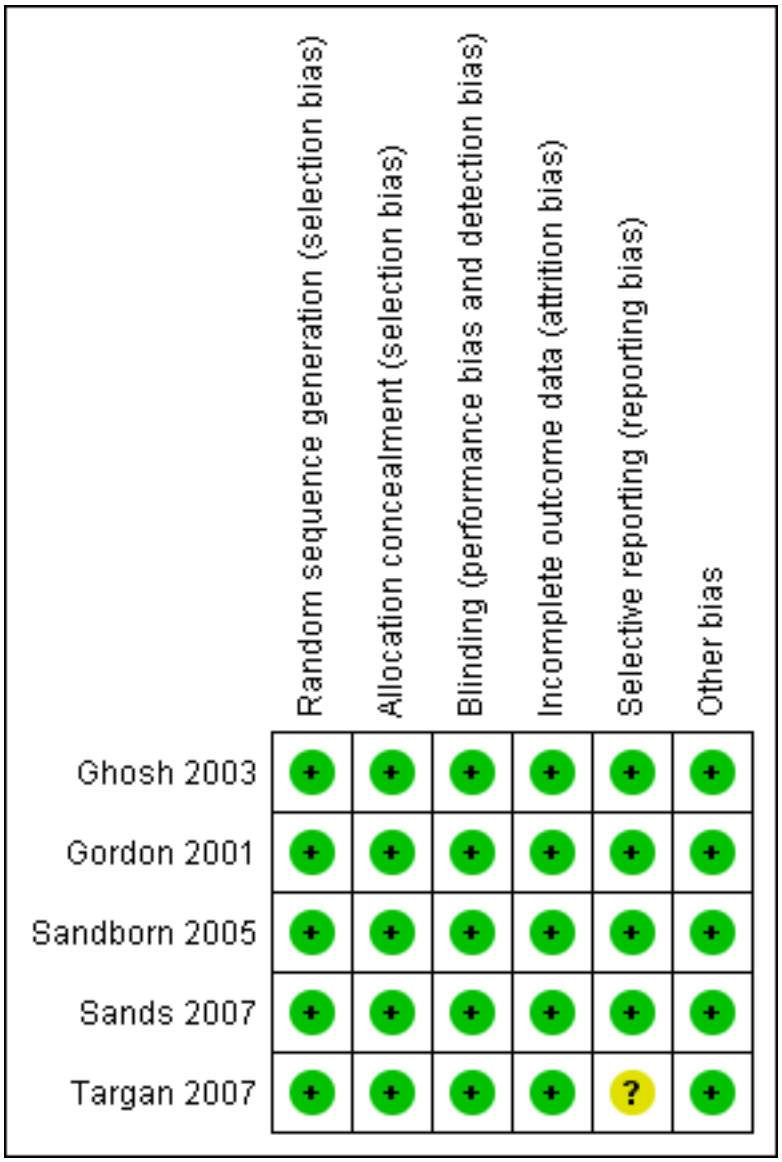
Excluded studies

One study was excluded (see Characteristics of excluded studies table). Kane 2012 was a prospective cohort study that reported on the authors' experience with natalizumab in clinical practice at the Mayo Clinic Rochester.

Risk of bias in included studies

The methodological quality of each trial was assessed using Cochrane risk of bias tool (Higgins 2011; See Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All of the studies used adequate methods for sequence generation and allocation concealment and were rated as low risk of bias for these items.

Blinding

All of the studies utilized adequate methods to ensure blinding and were rated as low risk of bias for this item.

Incomplete outcome data

For all of the included studies patient withdrawals were described and reasons for withdrawal were distributed evenly across treatment groups. All of the studies were rated as low risk of bias for incomplete outcome data.

Selective reporting

Four of the included studies reported on all expected outcomes and were rated as low risk of bias for this item. Targan 2007 did not report on the mean change in SF-36 and its components. The SF-36 is a generic quality of life instrument and this was a secondary outcome. However, the authors did report on the mean change in IBDQ from baseline. The IBDQ is an IBD specific quality of life instrument. We rated Targan 2007 as unclear risk of bias for selective reporting.

Other potential sources of bias

All of the included studies appeared to be free from other potential sources of bias and were rated as low risk of bias for this item.

Effects of interventions

See: **Summary of findings for the main comparison** One infusion of natalizumab (300 mg or 3 mg/kg) compared to placebo for

induction of remission in Crohn's disease; **Summary of findings 2** Two infusions of natalizumab (300 mg or 3 mg/kg) compared to placebo for induction of remission in Crohn's disease; **Summary of findings 3** Two infusions of natalizumab (6 mg/kg) compared to placebo for induction of remission in Crohn's disease; **Summary of findings 4** Three infusions of natalizumab (300 mg) compared to placebo for induction of remission in Crohn's disease; **Summary of findings 5** Three infusions of natalizumab (300 mg) and two infusions of infliximab (5 mg/kg) compared to placebo and two infusions of infliximab for induction of remission in Crohn's disease

One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo

Failure to induce remission at two weeks:
Data from three randomized trials were available for this outcome (Ghosh 2003**;** Gordon 2001**;** Sandborn 2005). A total of 1132 patients were enrolled in the three trials with 876 randomized to receive one infusion of natalizumab (300 mg or 3 mg/kg) and 256 to placebo. Participants in the natalizumab group were significantly less likely to fail to enter remission than placebo patients. After two weeks, 85% (745/876) of patients in the natalizumab group failed to enter remission compared to 90% (231/256) of the placebo group (RR 0.94, 95% CI 0.89 to 0.98, GRADE moderate quality). The risk difference was calculated to be -0.06 (95% CI -0.10 to -0.01). The number needed to treat for an additional beneficial outcome (NNTB) was 17.

Failure to induce remission at four weeks:
Data from three randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005; Targan 2007). A total of 1611 patients were enrolled in the three trials with 1117 randomized to one infusion of natalizumab (300 mg or 3 mg/kg) and 494 to placebo. Participants in the natalizumab group were significantly less likely to fail to enter remission than placebo patients. After four weeks, 76% (849/1117) of patients in the natalizumab group failed to enter remission compared to 83% (411/494) of the placebo group (RR 0.91, 95% CI 0.86 to 0.96, GRADE high quality). The risk difference was calculated to be -0.07 (95% CI -0.12 to -0.01). The NNTB was 15.

Failure to induce clinical response at two weeks:
Data from two randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005). There was no statistically significant difference in clinical response rates at two weeks. After two weeks, 58% (502/858) of patients in the natalizumab group failed to have a clinical response to treatment compared to 68% (166/244) of placebo patients (RR 0.82, 95% CI 0.66 to 1.01, GRADE moderate quality).

Failure to induce clinical response at four weeks:
Data from three randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005; Targan 2007). Participants in the natalizumab group were significantly less likely to fail to have a clinical response than placebo patients. After four weeks, 49% (543/1117) of patients in the natalizumab group failed to have a clinical response to treatment compared to 61% (303/494) of placebo patients (RR 0.78, 95% CI 0.66 to 0.92, GRADE moderate quality). The risk difference was calculated to be -0.14 (95% CI -0.24 to -0.04). The NNTB was 8.

Mean CDAI:
The Ghosh 2003 and Sandborn 2005 studies reported baseline CDAI scores but did not report on mean change in CDAI from baseline. The Gordon 2001 study reported mean CDAI scores with ranges which did not allow for meta-analysis. The Targan 2007 study reported on change in mean CDAI scores at week four after one infusion of natalizumab or placebo. At four weeks, patients in the natalizumab group had a significantly greater change in CDAI from baseline compared to patients in the placebo group. At four weeks, the mean change in CDAI from baseline was -83 in the natalizumab group compared to -50.1 in the placebo group (MD -32.90, 95% CI -47.85 to -17.95).

Adverse events:
One trial reported on the proportion of patients with adverse events, withdrawals due to adverse events and serious adverse events up to week 12 in patients who received one infusion of natalizumab (3 mg/kg) or placebo (Ghosh 2003). The proportion of patients who had an adverse event was similar in each group. Seventy-four per cent (50/68) of natalizumab patients had at least one adverse event compared to 81% (51/63) of placebo patients (RR 0.91, 95% CI 0.75 to 1.09, GRADE moderate quality). Commonly reported adverse events included abdominal pain, arthralgia, colitis, influenza syndrome, headache, infection, nausea, pain, pharyngitis and the development of antibodies to natalizumab. There was no significant difference in withdrawals due to adverse events. One of 68 (1.5%) patients treated with natalizumab withdrew due to adverse events compared to 2 of 63 (3.2%) placebo patients (RR 0.46, 95% CI 0.04 to 4.98, GRADE low quality). There was no significant difference in the proportion of patients who had a serious adverse event. Ten per cent (7/68) of natalizumab patients withdrew due to an adverse event compared to 11% (7/63) of placebo patients (RR 0.93, 95% CI 0.34 to 2.49, GRADE low quality). Serious adverse events including worsening of Crohn's disease and complications due to Crohn's disease. There were no reported cases of PML.

Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo

Failure to induce remission at six weeks:
Data from two randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005). A total of 1034 patients were enrolled in the two trials with 790 randomized to two infusions of natalizumab (300 mg or 3 mg/kg) and 244 to placebo. Natalizumab patients were significantly less likely than placebo patients to fail to enter remission at six weeks. After six weeks, 66% (523/790) of natalizumab patients failed to enter remission compared to 76% (186/244) of the placebo group (RR 0.85, 95% CI 0.78 to 0.93, GRADE high quality). The risk difference was calculated to be -0.11 (95% CI -0.18 to -0.05). The NNTB was 10.

Failure to induce remission at eight weeks:
Data from three randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005; Targan 2007). A total of 1543 patients were enrolled in the three trials with 1049 randomized to two infusions of natalizumab (300 mg or 3 mg/kg) and 494 to placebo. Natalizumab patients were significantly less likely than placebo patients to fail to enter remission at eight weeks. After eight weeks, 66% (693/1049) of patients in the natalizumab group failed to enter remission compared to 77% (382/494) of patients in the placebo group (RR 0.85, 95% CI 0.76 to 0.95; GRADE moderate quality). The risk difference was calculated to be -0.12 (95% CI -0.21 to -0.04). The NNTB was 9

Failure to induce clinical response at six weeks:

Data from two randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005). There was no significant difference in clinical response rates at six weeks. After six weeks, 41% (324/790) of patients in the natalizumab group failed to have a clinical response to treatment compared to 51% (125/244) of patients in the placebo group (RR 0.66, 95% CI 0.35 to 1.25, GRADE low quality). A high degree of heterogeneity was detected for this outcome (I^2 = 87%).

Failure to induce clinical response at eight weeks:
Data from three randomized trials were available for this outcome (Ghosh 2003; Sandborn 2005; Targan 2007). Natalizumab patients were significantly less likely than placebo patients to fail to have a clinical response at eight weeks. After eight weeks 43% (448/1049) of patients in the natalizumab group failed to have a clinical response to treatment compared to 57% (282/494) of patients in the placebo group (RR 0.73, 95% CI 0.58 to 0.91; GRADE low quality). A moderate degree of heterogeneity was detected for this comparison (I^2 = 68%) The risk difference was calculated to be -0.16 (95% CI -0.28 to -0.05). The NNTB was 7.

Mean CDAI:
Targan 2007 reported on change in mean CDAI scores at week eight after two infusions of natalizumab or placebo. At eight weeks, patients in the natalizumab group had a significantly greater change in CDAI from baseline compared to patients in the placebo group. At eight weeks, the mean change in CDAI from baseline was -104.4 in the natalizumab group compared to -65.8 in the placebo group (MD -38.60, 95% CI -55.26 to -21.94).

Adverse events:
One trial reported on the proportion of patients with adverse events, withdrawals due to adverse events, and serious adverse events up to week 12 for patients who received two infusions of natalizumab (3 mg/kg) or placebo (Ghosh 2003). The proportion of patients who had an adverse event was similar in each group. Eighty-six per cent (57/66) of natalizumab patients had at least one adverse event compared to 81% (51/63) of placebo patients (RR 1.07, 95% CI 0.92 to 1.24, GRADE moderate quality). There was no significant difference in withdrawals due to adverse events. Three per cent (2/66) of natalizumab patients withdrew due to an adverse event compared to 3% (2/63) of placebo patients (RR 0.95, 95% CI 0.14 to 6.57, GRADE low quality). There was no significant difference in serious adverse events. Serious adverse events were reported for 9% (6/66) of patients in the natalizumab group compared to 11% (7/63) of placebo patients (RR 0.82, 95% CI 0.29 to 2.30, GRADE low quality). There were no reported cases of PML.

Two infusions of natalizumab (6 mg/kg) versus placebo

Failure to induce remission at six weeks:
Data from one randomized trial were available for this outcome (Ghosh 2003). A total of 114 patients were enrolled in this arm of the trial with 51 randomized to two infusions of natalizumab (6 mg/kg) and 63 to placebo. There was no significant difference in remission rates at six weeks. After six weeks, 69% (35/51) of patients in the natalizumab group failed to enter remission compared to 73% (46/63) of patients in the placebo group (RR 0.94, 95% CI 0.74 to 1.19, GRADE moderate quality).

Failure to induce remission at eight weeks:
Natalizumab patients were significantly less likely than placebo patients to fail to enter remission at eight weeks. After eight weeks, 57% (29/51) of patients in the natalizumab group failed to enter remission compared to 84% (53/63) of the placebo group (RR 0.68, 95% CI 0.52 to 0.88, GRADE moderate quality). The risk difference was calculated to be -0.27 (95% CI -0.44 to -0.11). The NNTB was four.

Failure to induce clinical response at six weeks:
There was no statistically significant difference in clinical response rates at six weeks. At week six, 43% (22/51) of patients in the natalizumab group failed to have a clinical response to treatment compared to 62% (39/63) of the placebo group (RR 0.70, 95% CI 0.48 to 1.01, GRADE moderate quality).

Failure to induce clinical response at eight weeks:
There was a statistically significant difference in clinical response rates at eight weeks. At week eight, 45% (23/51) of patients in the natalizumab group failed to have a clinical response to treatment compared to 65% (41/63) of the placebo group (RR 0.69, 95% CI 0.49 to 0.99, GRADE moderate). The risk difference was calculated to be -0.20 (95% CI -0.38 to -0.02). The NNTB was five.

Adverse events:
One trial reported on the proportion of patients with adverse events, withdrawals due to adverse events and serious adverse events up to week 12 for patients who received two infusions of natalizumab (6 mg/kg) or placebo (Ghosh 2003). There was no significant difference in the proportion of patients who had an adverse event. Seventy-eight per cent (40/51) of natalizumab patients had at least one adverse event compared to 81% (51/63) of placebo patients (RR 0.97, 95% CI 0.80 to 1.17, GRADE moderate quality). There was no significant difference in withdrawals due to adverse events. Six per cent (3/51) of patients treated with natalizumab withdrew due to adverse events compared to 3% (2/63) of placebo patients (RR 1.85, 95% CI 0.32 to 10.67, GRADE low quality). Serious adverse event rates were similar in both groups. Twelve per cent (6/51) of natalizumab patients had a serious adverse event compared to 11% (7/63) of placebo patients (RR 1.06, 95% CI 0.38 to 2.95, GRADE low quality). There were no reported cases of PML.

Three infusions of natalizumab (300 mg) versus placebo

Failure to induce remission at ten weeks:
Data from one randomized trial were available for this outcome (Sandborn 2005). A total of 905 patients were enrolled in this arm of the trial with 724 randomized to three infusions of natalizumab (300 mg) and 181 to placebo. There was no statistically significant difference in the proportion of patients who failed to enter remission at week 10. After ten weeks, 63% (457/724) of patients in the natalizumab group failed to enter remission compared to 70% (126/181) of the placebo group (RR 0.91, 95% CI 0.81 to 1.01, GRADE high quality). Sandborn 2005 reported some post hoc subgroup analyses for patients with active inflammation or chronically active disease despite conventional therapy. These subgroups consisted of patients with elevated CRP at baseline, patients with active disease despite the use of immunosuppressants and patients who had prior anti-TNF-α therapy. The subgroup analyses demonstrated statistically significant differences in remission at ten weeks favouring three infusions of natalizumab (300 mg) over placebo for patients with an elevated CRP at baseline (RR 0.83, 95% CI 0.73 to 0.94; NNTB = 9, P = 0.004), for patients using immunosuppressants (RR 0.80, 95% CI 0.67 to 0.96, P = 0.02) and for

patients previously treated with anti-TNF-α therapy (RR 0.85, 95% CI 0.73 to 0.98; NNTB = 9, P = 0.02).

Failure to induce remission at twelve weeks:
Data from two randomized trials were available for this outcome (Sandborn 2005; Targan 2007). A total of 1414 patients were enrolled in the two trials with 983 randomized to three infusions of natalizumab (300 mg) and 431 to placebo. Natalizumab patients were significantly less likely to fail to enter remission at 12 weeks than placebo patients. After twelve weeks, 61% (596/983) of patients in the natalizumab group failed to enter remission compared to 73% (313/431) of the placebo group (RR 0.85, 95% CI 0.78 to 0.98, GRADE high quality). The risk difference was calculated to be -0.11 (95% CI -0.16 to -0.05). The NNTB was 10. Post hoc subgroup analyses reported by Sandborn 2005 demonstrated statistically significant differences in remission at twelve weeks favouring three infusions of natalizumab (300 mg) over placebo for patients with an elevated CRP at baseline (RR 0.81, 95% CI 0.71 to 0.92; NNTB = 8, P = 0.002), for patients using immunosuppressants (RR 0.79, 95% CI 0.65 to 0.96; NNTB = 7, P = 0.02) and for patients previously treated with anti-TNF-α therapy (RR 0.85, 95% CI 0.73 to 0.98; NNTB = 9, P = 0.02).

Failure to induce clinical response at ten weeks:
Data from one randomized trial were available for this outcome (Sandborn 2005). After ten weeks, 44% (316/724) of patients in the natalizumab group failed to have a clinical response to treatment compared to 51% (93/181) of the placebo group (RR 0.85, 95% CI 0.72 to 1.00, GRADE high quality). Post hoc subgroup analyses reported by Sandborn 2005 demonstrated statistically significant differences in clinical response at ten weeks favouring three infusions of natalizumab (300 mg) over placebo for patients with an elevated CRP at baseline (RR 0.76, 95% CI 0.63 to 0.91; NNTB = 8, P = 0.003), for patients using immunosuppressants (RR 0.67, 95% CI 0.51 to 0.89; NNTB = 6, P = 0.006) and for patients previously treated with anti-TNF-α therapy (RR 0.68, 95% CI 0.55 to 0.84; NNTB = 5, P = 0.0004). This outcome received an overall GRADE analysis rating of high.

Failure to induce clinical response at twelve weeks:
Data from two randomized trials were available for this outcome (Sandborn 2005; Targan 2007). Natalizumab patients were significantly less likely to fail to have a clinical response at 12 weeks than placebo patients. After twelve weeks, 39% (387/983) of natalizumab patients failed to respond to treatment compared to 53% (229/431) of placebo patients (RR 0.76, 95% CI 0.67 to 0.86, GRADE high quality). The risk difference was calculated to be -0.13 (95% CI -0.19 to -0.07). The NNTB was eight. Post hoc subgroup analyses reported by Sandborn 2005 demonstrated statistically significant differences in clinical response at twelve weeks favouring three infusions of natalizumab (300 mg) over placebo for patients with an elevated CRP at baseline (RR 0.71, 95% CI 0.58 to 0.86; NNTB = 7, P = 0.0006), for patients using immunosuppressants (RR 0.68, 95% CI 0.51 to 0.91; NNTB = 6, P = 0.01) and for patients previously treated with anti-TNF-α therapy (RR 0.67, 95% CI 0.53 to 0.83, P = 0.0004).

Mean CDAI:
Targan 2007 reported on change in mean CDAI scores at week twelve eight after three infusions of natalizumab or placebo. At 12 weeks, patients in the natalizumab group had a significantly greater change in CDAI from baseline compared to patients in the placebo group. At 12 weeks, the mean change in CDAI from baseline was -117.9 in the natalizumab group compared to -68.3 in the placebo group (MD -49.60, 95% CI -67.35 to -31.85).

Adverse events:
Two trials reported on the proportion of patients with adverse events, withdrawals due to adverse events, and serious adverse events in patients who received three infusions of natalizumab (300 mg) or placebo (Sandborn 2005; Targan 2007). There were no statistically significant differences in adverse event rates at week 12 for any of these outcomes. Eighty-six per cent (848/984) of natalizumab patients had at least one adverse event compared to 83% (359/431) of placebo patients (RR 1.03, 95% CI 0.98 to 1.08, GRADE high quality). Common adverse events included headache (Sandborn 2005; Targan 2007), nausea (Sandborn 2005; Targan 2007), nasopharyngitis (Sandborn 2005; Targan 2007), abdominal pain (Sandborn 2005), fatigue (Sandborn 2005), vomiting (Sandborn 2005) and exacerbation of Crohn's disease (Sandborn 2005; Targan 2007). Eight per cent (82/984) of natalizumab patients withdrew due to adverse events compared to 10% (45/431) of placebo patients (RR 0.86, 95% CI 0.59 to 1.26, GRADE moderate quality). Six per cent (65/983) of natalizumab patients had a serious adverse event compared to 8% (36/431) of placebo patients (RR 0.76, 95% CI 0.37 to 1.56, GRADE low quality). There were no reported cases of PML.

Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab

Failure to induce clinical remission at week 10:
Data from one randomized trial were available for this outcome (Sands 2007). There was no statistically significant difference in remission rates at ten weeks. Sixty-four per cent (33/52) of patients assigned to combined biologic therapy failed to achieve remission compared to 70% (19/27) assigned to placebo and infliximab at week 10 (RR 0.90, 95% CI 0.65 to 1.24, GRADE moderate quality). This outcome was reported as a secondary endpoint. Sands 2007 conducted a post hoc subgroup analysis on patients with elevated CRP at baseline which revealed a statistically significant difference in remission rates between groups. At week 10, 71% (17/24) of patients assigned to natalizumab and infliximab failed to achieve clinical remission, whereas all 11 patients assigned to placebo and infliximab failed to do so (RR 0.73, 95% CI 0.55 to 0.97, P = 0.03). The risk difference was calculated to be -0.29 (95% CI -0.50,-0.08), corresponding to a NNTB of 4.

Mean CDAI:
Sands 2007 reported on mean changes in CDAI from baseline but did not report the standard deviations. At week six, the mean CDAI in the combined biologic group decreased 37.7 points compared to a decrease of 3.5 points in the group receiving placebo and infliximab (P = 0.084).

Adverse events:
There was no statistically significant difference in the proportion of patients who had an adverse event. Ninety-two per cent (48/52) of patients in the combined biologic therapy group had at least one adverse event compared to 100% (27/27) of patients in the placebo-infliximab group (RR 0.93, 95% CI 0.85 to 1.03; GRADE moderate quality). Common adverse events included headache, exacerbation of Crohn's disease, nausea, and nasopharyngitis. No opportunistic infections or lymphomas were reported although the size and duration of this study were not adequate for detecting serious but rare adverse events.

Patients receiving natalizumab-infliximab therapy and placebo-infliximab therapy were at similar risk of experiencing serious adverse events and adverse events leading to withdrawal. Two per cent (1/52) of patients in the combined biologic therapy group had a serious adverse event compared to 4% (1/27) of patients in the placebo-infliximab group (RR 0.52, 95% CI 0.03 to 7.98, GRADE low quality). Serious adverse events included intestinal obstruction and exacerbation of Crohn's disease. No patients in the combined biologic therapy group withdrew due to adverse events compared to 4% (1/27) in the placebo-infliximab group (RR 0.18, 95% 0.01 to 4.18, GRADE low quality). There were no reported cases of PML.

DISCUSSION

Summary of main results

Although current therapies for Crohn's disease provide benefit, they do not effectively control the disease in many patients. Most therapies are also limited by adverse event profiles. Thus, there is a need for effective and safe treatment that can induce clinical response and remission. Pooled data from four included studies suggest that natalizumab (300 mg and weight based doses of 3 mg/kg) is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease (Ghosh 2003; Gordon 2001; Sandborn 2005; Targan 2007). This benefit is statistically significant for both short and long term treatment. There was a trend toward increased benefit with additional infusions of natalizumab.

One infusion of natalizumab was significantly superior to placebo for induction of remission at two (NNTB 17) and four weeks (NNTB 15) and for induction of clinical response at 4 weeks (NNTB 8). Two infusions of natalizumab (300 mg or 3 mg/kg) were significantly superior to placebo for induction of remission at six weeks (NNTB 10) and eight weeks follow-up (NNTB 9). Although, three infusions of natalizumab (300 mg) were significantly superior to placebo for induction of remission (NNTB 10) and clinical response (NNTB 8) at twelve weeks follow-up these comparisons were not statistically significant at ten weeks follow-up. The proportion of patients with a clinical response at ten weeks was the primary efficacy end point for the ENACT-1 trial (Sandborn 2005). At ten weeks 49% of the placebo group had a clinical response compared to 56% of the natalizumab group (P = 0.051). The relatively high placebo response rate may have made it difficult to observe a treatment effect. This may be a consequence of the study design: the 4 to 1 randomization ratio may have led patients to believe that they would be assigned to active therapy and thus experience a beneficial effect. Another possibility is that some of the patients may not have had active inflammation at study entry. This possibility is consistent with the findings of post hoc subgroup analyses where natalizumab appears to convey greater benefit for patient subgroups characterized by objective confirmation of active inflammation or chronically active disease despite conventional therapies. These post hoc subgroup analyses demonstrated significantly greater clinical response and remission rates for natalizumab compared with placebo in patients with elevated CRP levels, active disease despite the use of immunosuppressants, or prior anti-TNF-α therapy. These benefits were apparent for both short term (one infusion) and longer term treatment (two or three infusions). Three infusions of natalizumab (300 mg) were significantly superior to placebo for induction of remission at ten and twelve weeks for patients with an elevated CRP at baseline (NNTB 9 and 8), for patients using immunosuppressants (NNTB 7 at weeks ten and twelve) and for patients previously treated with anti-TNF-α therapy (NNTB 9 at weeks ten and twelve). Three infusions of natalizumab (300 mg) were significantly superior to placebo for induction of clinical response at ten and twelve weeks for patients with an elevated CRP at baseline (NNTB 8 and 7), for patients using immunosuppressants (NNTB 6 at weeks ten and twelve) and for patients previously treated with anti-TNF-α therapy (NNTB 5 at weeks ten and twelve).

The ENCORE study enrolled 509 patients with an elevated CRP level (Targan 2007). This trial met both primary and secondary endpoints. Three infusions of natalizumab (300 mg) were significantly superior to placebo for induction of clinical response at both weeks eight and twelve (NNTB 7). Three infusions of natalizumab (300 mg) were also significantly superior to placebo for induction of clinical remission at both weeks eight and twelve (NNTB 10). Natalizumab was also found to be significantly superior to placebo for induction of clinical response ($P < 0.001$) and remission ($P \leq 0.009$) at all assessments (weeks 4, 8 and 12). Targan 2007 concluded that these data support the efficacy of natalizumab as induction therapy for Crohn's disease.

The small safety and tolerability study by Sands 2007 suggests that combining three natalizumab with two injections of infliximab is safe and tolerable over a 10 week period. With 79 patients enrolled, this study was only powered to detect differences in the rate of adverse events at least 80% of the time given that they occur at a frequency of 3.9% or more. This raises the issue of potential type II error in detecting rare but serious adverse events which are known to be associated with natalizumab and infliximab; as such, the safety data from this study should be interpreted with caution. The study was unable to detect a statistically significant difference in therapeutic efficacy within the pooled study population but post hoc subgroup analyses suggest that patients with elevated CRP at baseline achieved greater rates of remission with natalizumab and infliximab combination therapy compared to infliximab alone.

The optimal dosage and timing schedule for induction of remission and response using natalizumab therapy remains to be determined. Ghosh 2003 looked at the efficacy of two different dosages of natalizumab in comparison to placebo and did not find any advantage for two infusions of 6 mg/kg natalizumab over 3 mg/kg natalizumab. The pooled data suggest that a doses of 300 mg or weight based doses of 3 mg/kg may be effective for induction of remission and clinical response in patients with moderately to severely active Crohn's disease. Three of the included studies dosed patients every four weeks for a total of two infusions (Ghosh 2003) and three infusions (Sandborn 2005; Targan 2007). No studies to date have tried to administer dosages using a different timing schedule.

The ENACT-1 trial did not enrol patients with fistulizing Crohn's disease (Sandborn 2005). Although the Gordon 2001 and Ghosh 2003 included patients with fistulizing Crohn's disease they did not make any comments on the efficacy of natalizumab for fistula healing and closure. To our knowledge, there are no published data on the efficacy of natalizumab for the treatment of Crohn's fistulas.

Natalizumab was generally well tolerated and the safety profile observed in the five included studies was similar. Adverse events occurred infrequently and were experienced by a similar proportion of natalizumab and placebo treated patients. There were no statistically significant differences in the proportions

of patients who withdrew due to adverse events or those who experienced serious adverse events up to week twelve in patients treated with one, two or three infusions of natalizumab (300 mg or to 3 mg/kg or 6 mg/kg) or placebo. For patients treated with three infusions of natalizumab (300 mg) or placebo there was no statistically significant difference in the proportion of patients who withdrew from the study for any reason. Targan 2007 reported that the incidence and types of adverse events were similar between groups. Adverse events experienced during the trials included: headache, worsening of Crohn's disease, abdominal pain, arthralgia, colitis, influenza syndrome, infection, nausea, vomiting, fatigue, pharyngitis, infusion reactions, hypersensitivity-like reactions and the development of antibodies against natalizumab. Concomitant use of immunosuppressive agents and corticosteroids may be protective against anti-natalizumab antibody formation (Sandborn 2005). However, one patient who received six natalizumab infusions with concurrent 6-mercaptothioprine therapy in Targan 2007 and a subsequent open-label extension was diagnosed with B-cell lymphoma. When persistent anti-natalizumab antibodies were present, these antibodies appear to be associated with infusion reactions, hypersensitivity-like reactions, and loss of efficacy (Sandborn 2005). None of the included studies reported tuberculosis or opportunistic infection related to natalizumab treatment but two malignancies in patients receiving natalizumab were reported by Targan 2007 (one basal cell carcinoma and the aforementioned B-cell lymphoma). There were no deaths reported in the Ghosh 2003 and Gordon 2001 studies. There were two deaths in the ENACT-1 trial in patients assigned to natalizumab. Neither of these deaths were attributed to treatment with natalizumab. The first patient died as a result of an occupational accident. The second patient died as a result of complications after surgery for a severe exacerbation of Crohn's disease 28 weeks after completing the ENACT-1 trial (Sandborn 2005).

All of the included trials lacked adequate power to detect rare but serious adverse events. In 2005, two patients with multiple sclerosis treated with natalizumab in combination with interferon beta-1a and one patient with Crohn's disease treated with natalizumab in combination with azathioprine developed PML resulting in two patient deaths (Kleinschmidt-Demasters 2005; Langer-Gould 2005; Van Assche 2005). The Crohn's patient received three doses of natalizumab in combination with azathioprine during ENACT-1, 9 doses of placebo in combination with azathioprine during ENACT-2 (maintenance trial) and five doses of natalizumab without concurrent azathioprine during an open label extension study (Sandborn 2005). PML is a serious opportunistic infection of the central nervous system for which there is no specific treatment. PML is caused by the reactivation of quiescent JC polyomavirus. In response to the problem the manufacturers of natalizumab (Biogen Idec and Elan Pharmaceuticals) in consultation with regulatory authorities and the National Institutes of Health conducted a retrospective investigation to assess the risk of PML in natalizumab treated patients (Yousry 2006). All adverse events were reviewed to identify any unrecognised occurrences of PML and exposed patients underwent neurological examination and MRI scanning. A total of 3826 patients who had participated in recent clinical trials of natalizumab for the treatment of multiple sclerosis, Crohn's disease or rheumatoid arthritis were recruited for the evaluation. The history and either physical examination or MRI were available for 3116 patients. Yousry 2006 estimated that the incidence of PML associated with exposure to natalizumab is 1.0 cases per 1000 patients (95% CI 0.2 to 2.8 per 1000) in this population who received a mean of 17.9 monthly doses of natalizumab. The investigation found no new confirmed cases of PML. In mid-2006, natalizumab was re-approved for the treatment of multiple sclerosis by the FDA with the condition that Biogen Idec and Elan aggressively monitor for adverse events associated with treatment. In 2008, natalizumab was approved by the FDA for the treatment of Crohn's. As of June 2017, Biogen 2017 reports 731 confirmed cases of PML, 24% of which were fatal, with an incidence of 4.21 per 1000 patients (95% CI 3.91 to 4.52 per 1000 patients).

Currently, there are no tests which can accurately predict the onset or occurrence of PML. PML has been shown to be more likely in those who have positive JC-virus antibodies, who have received immunosuppression, and have had longer duration of treatment (Bloomgren 2012). Natalizumab is known to cause movement of B-cells, a JC virus reservoir, from the bone marrow to the peripheral circulation by disrupting localization signals (Andrian 2003). Adelman 2005 and Berger 2005 suggested that the prospective measurement of the JC viral load in plasma and the reduction or discontinuation of natalizumab treatment if JC virus is detected in the blood might prevent the development of PML in this setting. However, a study of 19 patients demonstrated that JC virus DNA increases in the blood or urine within 12 months of initiating natalizumab therapy (Chen 2009), and that neither parameter was linked to a meaningful clinical outcome. The manufacturer recommends screening for JC virus antibodies prior to initiating and during treatment. The wide prevalence of nonsymptomatic JC viremia and viremia coupled with the rarity of PML makes establishing a statistical relationship a difficult task. Alternatively, vedolizumab, a gut selective α4ß7 integrin antibody (Soler 2009), is an option for induction and maintenance of Crohn's disease (Sandborn 2013). To date, there have been no reported cases of PML associated with vedolizumab and minimal adverse outcomes reported (Colombel 2016).

In summary, high quality data suggest that natalizumab is effective for induction of clinical remission and response in some patients with moderately to severely active Crohn's disease. However, none of the included studies had the power to detect rare but serious adverse events. such as PML. Due to the association with PML, and the availability of alternative agents that are not associated with PML, natalizumab is not likely to be used in patients who fail currently available medical therapy. The use of natalizumab in select patients (e.g. patients allergic to different biologics) needs to be carefully considered against the potential risk of developing PML. Futher studies of natalizumab are not likely to be done.

Overall completeness and applicability of evidence

This review included five studies with a total of 1771 participants. However, some comparisons of interest such as safety (i.e.. adverse events, serious adverse events) only included a low number of participants and low number of events. The results of this meta-analysis are applicable to people with moderate to severe Crohn's disease.

Quality of the evidence

Four included studies were judged to be at low risk of bias (Ghosh 2003; Gordon 2001; Sandborn 2005; Sands 2007). Targan 2007 was assessed as unclear risk of bias for selective reporting. This study did not report on a secondary outcome change in SF-36 scores from

baseline. The SF-36 is a generic quality of life tool that is used for many different health conditions. Although Targan 2007 did not report on this outcome, it did report on change in IBDQ scores from baseline. The IBDQ is a validated IBD-specific quality of life tool. Targan 2007 was judged to be at low risk of bias for all other items.

GRADE analyses indicated that overall quality of evidence supporting the primary outcome, 'induction of remission' ranged from moderate to high for most comparisons with high quality evidence of benefit with more infusions of natalizumab. Reasons for downgrading included inconsistency and imprecision. GRADE analyses indicated that overall quality of evidence supporting the secondary outcome clinical response ranged from low to high with higher quality evidence available for more infusions of natalizumab. Reasons for downgrading included inconsistency and imprecision. GRADE analyses indicated that the overall quality of evidence for the secondary outcome adverse events ranged from moderate to high with higher quality evidence available for more infusions of natalizumab. Reasons for downgrading included inconsistency and imprecision. The overall quality of the evidence supporting the secondary outcomes withdrawal due to adverse events and serious adverse events was generally low due to serious imprecision. The evidence from the one small study (N = 79) that assessed combined therapy with natalizumab and infliximab compared to infliximab and placebo was moderate for induction of remission and adverse events and low for withdrawal due to adverse events and serious adverse events. All outcomes from this study were downgraded due to imprecision.

Potential biases in the review process

We performed a comprehensive literature search to minimize bias related to study selection. In a effort to reduce bias, two authors (SMLN and TMN) independently reviewed studies for inclusion and exclusion, extracted data, and assessed study quality. All five of the included studies were funded by Elan pharmaceuticals or Biogen Idec, the manufacturers of natalizumab. Pharmaceutical consultants, employees, and shareholders also had varying degrees of participation during trial design, data analysis, and manuscript editing. While such industry involvement represents an important source of support for large, multi-centre trials such as the ones included in this review, studies sponsored by pharmaceutical companies are more likely to have an outcome favouring the sponsor than were studies funded by other sponsors (Lexchin 2003). Given that positive outcomes predominated the results of the included studies, these results should be interpreted with caution.

Agreements and disagreements with other studies or reviews

We found three systematic reviews that assessed the use of natalizumab (Chandar 2015), or anti-integrins in Crohn's disease (Ge 2015; Lin 2015). All of these reviews came to similar conclusions as our review. Chandar 2015 included the same five natalizumab studies that were included in our systematic review and concluded that natalizumab and vedolizumab (also an anti α4 integrin drug) are effective for inducing remission and response in patients with Crohn's disease, with similar efficacy in anti-TNF-α exposed and naive patients. We did not address prior ant-TNF-α exposure in our review as this was not a pre-specified subgroup analysis. Furthermore, Chandar 2015 pooled studies with different treatment regimens and drugs. This included pooling studies with different numbers of infusions of natalizumab (Ghosh 2003; Gordon 2001; Sandborn 2005; Targan 2007), and the study that compared combined biologic therapy (natalizumab and infliximab) to infliximab and placebo (Sands 2007). The authors also pooled studies of natalizumab and vedolizumab together. In our systematic review, we were careful to only pool studies with similar dosing regimens and therapies. Chandar 2015 also concluded that natalizumab is not likely to be used in Crohn's patients with moderate to severe disease given the availability of other agents such as vedolizumab that are not associated with the development of PML.

Despite searching several databases from 1990 to 2014, the systematic review by Ge 2015 only included three natalizumab studies (Ghosh 2003; Gordon 2001; Targan 2007). The authors concluded that integrin antagonists are efficacious and safe for treatment of Crohn's disease. Similar to the Chandar 2015 systematic review, studies with different dosing regimens and different drugs (i.e. natalizumab and vedolizumab) were pooled for meta-analysis. This review is also problematic as it includes unit of analysis errors in the pooled analyses. The systematic review by Lin 2015 included four natalizumab studies (Ghosh 2003; Gordon 2001; Sandborn 2005; Targan 2007), but sought to exclude studies where patients received combined therapy with other biologics. Lin 2015 concluded that anti-integrins show promise as a therapy for inflammatory bowel disease. Similar to the other reviews, this systematic review pooled studies with different dosing regimens and different drugs (natalizumab and vedolizumab).

AUTHORS' CONCLUSIONS

Implications for practice

High quality data suggest that natalizumab is effective for induction of clinical remission and response in some patients with moderately to severely active Crohn's disease. However, none of the included studies had the power to detect rare but serious adverse events such as PML. Due to the association with PML, and the availability of alternative agents that are not associated with PML, natalizumab is not likely to be used in patients who fail currently available medical therapy. The use of natalizumab in select patients (e.g. patients allergic to different biologics) needs to be carefully considered against the potential risk of developing PML.

Implications for research

Given the availability of alternate medications that are not associated with PML, natalizumab is unlikely to be used in patients with moderate to severe Crohn's disease. Futher studies of natalizumab are not likely to be done.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ghosh 2003

Methods	Randomized, double-blind, placebo-controlled, multi-center, 12 week induction trial Computer generated, site stratified, block randomization schedule
Participants	248 adult patients (≥ 18 years) with moderate to severe Crohn's disease (CDAI ≥ 220 to ≤ 450) Stable dose of AZA or 6-MP required for at least 4 months Exclusion criteria: MTX, CYA, or ID within 3 months prior to entry, prior treatment with antibody agent, oral prednisolone (> 25 mg/day) or equivalent, elemental or parenteral nutrition, infectious or neoplastic bowel disease, bowel surgery within 3 months, ostomy, fibrotic strictures, need for abdominal surgery
Interventions	Each group received an infusion at week zero and week four Treatment groups: two infusions of placebo (n = 63), one infusion of natalizumab (3 mg/kg) and one infusion of placebo (n = 68), two infusions of natalizumab 3 mg/kg; n = 66) and two infusions of natalizumab (6 mg/kg; n = 51)
Outcomes	The primary outcome variable was remission at week six (CDAI < 150) Secondary outcomes: clinical response (≥ 70 point decrease in CDAI from baseline), serum level of CRP, absolute neutrophil counts, serum antibodies against natalizumab and IBDQ Patients were evaluated at baseline and weeks two, four, six, eight, and twelve
Notes	Industry-involvement: funded by Elan pharmaceuticals, some authors were employees or paid consultants for Elan, some owned company equity
Risk of bias	

Ghosh 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, site-stratified, block randomization schedule
Allocation concealment (selection bias)	Low risk	Centrally randomized
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind - neither the study personnel nor the patients were aware of treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient withdrawals were described and distributed evenly across treatment groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Gordon 2001

Methods	Randomized, double-blind, placebo-controlled, multi-center, 12 week induction trial Table of random numbers
Participants	30 adult patients with mild to moderate Crohn's disease (CDAI of ≥ 151 and ≤ 450) Oral corticosteroids (≤ 40 mg prednisolone or ≤ 9 mg budesonide per day) permitted if dose was stable within 2 weeks of entry 5-ASA, AZA or 6-MP permitted provided treatment was not started within 2 months or the dose increased within 4 months of entry Female patents had to use contraception Exclusion criteria: pregnancy or breast feeding, weight > 100 kg, CDAI > 450 or inpatient due to Crohn's, patients treated with CYA, MTX or TAC, abdominal surgery within 3 months of entry or need for surgery, ileostomy or colostomy, laboratory-confirmed intestinal infection, malignant neoplasm
Interventions	Patients received one infusion of natalizumab (3 mg/kg; n = 18) or placebo (n = 12)
Outcomes	The primary outcome was the change in mean CDAI at two weeks post-infusion Secondary outcomes: remission (CDAI < 150), IBDQ, serum levels of CRP, ESR, blood count, peripheral blood T cells and B cells, serum natalizumab and anti-natalizumab antibody concentrations Patients were evaluated at study entry and at weeks one, two, four, eight and twelve post-infusion
Notes	Industry-support: funded by Elan pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement

Gordon 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Individual randomization concealment codes were held by the trial's sponsor and each hospital's pharmacy for emergency use, and none were opened during the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: investigators and patients remained blinded to the randomization codes until data analysis was complete
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient withdrawals were described and distributed evenly across treatment groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sandborn 2005

Methods	Randomized, double-blind, placebo-controlled, multi-center, 12 week induction trial Randomization was performed centrally and prospectively stratified by disease activity (CDAI < 330 versus CDAI ≥ 330) and concurrent corticosteroid therapy A pharmacist prepared each infusion of natalizumab or an identical placebo
Participants	905 adult patients with moderate to severe Crohn's disease (CDAI 220 to 450) Concomitant medication: stable doses of 5-ASA drugs, prednisone (≤ 25 mg/day), budesonide, AZA, 6-MP, MTX and antibiotics were permitted Exclusion criteria: short bowel syndrome, ostomy, total colectomy, stricture with obstructive symptoms, draining fistulas, abdominal abscess, previous natalizumab treatment or had received anti-TNF-α therapy within 3 months prior to entry
Interventions	Patients received an infusion of 300 mg of natalizumab (n = 724) or placebo (n = 181) for a total of three infusions given at weeks zero, four and eight
Outcomes	Primary and secondary outcomes were measured at week 10 The primary outcome was clinical response (≥ 70 point reduction in CDAI from baseline) Secondary outcomes: remission (CDAI < 150 points), serum levels of CRP, mean lymphocyte counts and IBDQ Patients were assessed at baseline and weeks two, four, six, eight, ten and twelve IBDQ was assessed at weeks zero, six and ten
Notes	Industry support: Funding provided by Elan pharmaceuticals, various authors report being employees, paid consultants, or shareholders of Elan
Risk of bias	

Sandborn 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Centrally randomized
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: pharmacist prepared each infusion of natalizumab or identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient withdrawals were described and distributed evenly across treatment groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sands 2007

Methods	Multicenter, randomized, double-blind, placebo-controlled 10 week induction trial was conducted at 17 sites in the United States
Participants	79 adult patients with at least a 6 month history of Crohn's with active disease (CDAI ≥ 150) receiving infliximab therapy Permitted concomitant medication: oral 5-ASA if on a stable dose for at least 4 weeks; stable dose oral antibiotics if on a stable dose for at least 4 weeks; oral corticosteroids (≤ 25 mg prednisolone or it's equivalent per day) for at least 4 weeks and at a stable dose of at least 2 weeks; azathioprine, 6-mercaptopurine, or methotrexate if on a stable dose for at least 8 weeks Exclusion criteria: bowel surgery within 3 weeks of entry, persistent intestinal obstruction, bowel perforation, uncontrolled bleeding, abdominal abscess, infection, symptoms largely a result of fibrotic strictures, neoplastic disease of the bowel, a positive stool culture for enteric pathogens at screening, nasogastric/nasoenteric tube feeding, an elemental diet, total parenteral nutrition within 2 weeks of week 0, significantly abnormal results of liver function tests at screening, and prior natalizumab therapy
Interventions	Patients received either 300 mg natalizumab (n = 52) or placebo (n = 27) every 4 weeks at weeks 0, 4, and 8, in addition to receiving an intravenous infliximab infusion (5 mg/kg) at week 6
Outcomes	The primary outcome was the safety and tolerability of natalizumab in patients with Crohn's disease concurrently receiving infliximab Secondary outcomes included therapeutic efficacy, health-related quality of life, the effects of natalizumab on markers of inflammation, and the effects of concurrent therapy
Notes	Industry support: Funding provided by Elan pharmaceuticals, various authors report being employees or paid consultants of Elan

Risk of bias

Bias	Authors' judgement	Support for judgement

Sands 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Centrally randomized
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: the placebo was identical in appearance to natalizumab, contained the same buffering solution, and infused over the same length of time
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient withdrawals were reported and distributed evenly across treatment groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Targan 2007

Methods	A phase III, randomized, double-blind, placebo-controlled , multi-center (114 sites), 12 week induction trial Permitted concurrent therapies for Crohn's disease: stable doses of 5-ASA, prednisone or an equivalent corticosteroid (20 mg/day), budesonide (6 mg/day), AZA, 6-MP, MTX, and antibiotics, were permitted Exclusion criteria: short-bowel syndrome, an ostomy, total colectomy, a stricture with obstructive symptoms, draining fistulas, an abdominal abscess, anti-TNF-α therapy within the previous 12 weeks, previous natalizumab therapy
Participants	509 patients with moderate to severely active Crohn's disease (CDAI ≥220 and ≤ 450) and evidence of active inflammation (CRP > 2.87 mg/L) Patients were randomized 1:1 to treatment with natalizumab or placebo infusions at weeks 0, 4, and 8 Efficacy and safety assessments were performed at weeks 4, 8, and 12
Interventions	Three infusions of intravenous natalizumab (300 mg, n = 259) or placebo (n = 250) at weeks 0, 4, and 8
Outcomes	The primary outcome variable was response by week eight which was defined as a reduction of ≥ 70 points in the CDAI score from baseline that sustained through week twelve Secondary outcome variables included the proportion of patients achieving response at week twelve, a clinical remission (defined as a CDAI score of less than 150) by week eight sustained to week twelve, and the proportion of patients with remission at week 12 Tertiary outcomes included proportion achieving a ≥ 100-point CDAI score decrease at weeks eight and twelve, achieving clinical response or remission at weeks four and eight, response at week eight, time to clinical remission, mean change in baseline CDAI, platelets and CRP at weeks four, eight and twelve, and to evaluate the effects of natalizumab on quality of life (IBDQ and SF-36) at week twelve
Notes	Industry support: Funded by Elan Pharmaceuticals, Inc and Biogen Idec. Various authors acted as paid consultants or employees for Elan or Biogen Idec
Risk of bias	

Targan 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally stratified
Allocation concealment (selection bias)	Low risk	Centrally randomized
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: the patients, site staff, and study investigators were all blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient withdrawals were reported as failures and were evenly distributed across treatment groups
Selective reporting (reporting bias)	Unclear risk	Most expected outcomes were reported Although the mean change in SF-36 and its components (a secondary outcome) was not reported the authors did report on the mean change in IBDQ from baseline
Other bias	Low risk	The study appears to be free of other sources of bias

CDAI: Crohn's disease activity index
AZA: azathioprine
6-MP: 6-mercaptopurine
MTX: methotrexate
CYA: cyclosporine
ID: investigational drug
CRP: C-reactive protein
IBDQ: Inflamatory Bowel Disease Questionnaire
5-ASA: 5-aminosalicylic acid
TAC: tacrolimus
ESR: erythrocyte sedimentation rate
anti-TNF-α: anti-tumour necrosis factor-alpha
SF-36: 36-Item Short Form Health Survey

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kane 2012	Prospective cohort study, not an RCT

RCT: randomized controlled trial

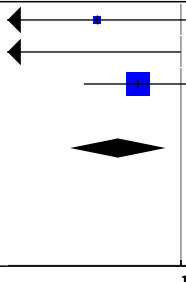
DATA AND ANALYSES

Comparison 1. One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce remission at 2 weeks	3	1132	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 0.98]
2 Failure to induce remission at 4 weeks	3	1611	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.96]
3 Failure to induce clinical response at 2 weeks	2	1102	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.01]
4 Failure to induce clinical response at 4 weeks	3	1611	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.66, 0.92]
5 Change in CDAI from baseline to 4 weeks	1	507	Mean Difference (IV, Fixed, 95% CI)	-32.9 [-47.85, -17.95]
6 Adverse events	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.09]
7 Withdrawal due to adverse events	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 4.98]
8 Serious adverse events up to week 12	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.34, 2.49]

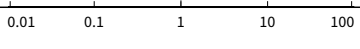
Analysis 1.1. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 1 Failure to induce remission at 2 weeks.

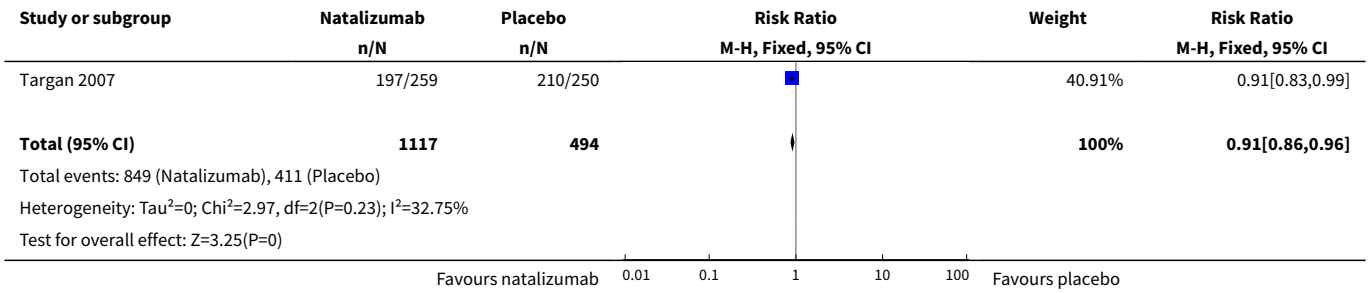
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ghosh 2003	111/134	57/63		22.06%	0.92[0.82,1.02]
Gordon 2001	11/18	11/12		3.75%	0.67[0.44,1]
Sandborn 2005	623/724	163/181		74.19%	0.96[0.9,1.01]
Total (95% CI)	**876**	**256**		**100%**	**0.94[0.89,0.98]**
Total events: 745 (Natalizumab), 231 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.35, df=2(P=0.19); I^2=40.26%					
Test for overall effect: Z=2.57(P=0.01)					



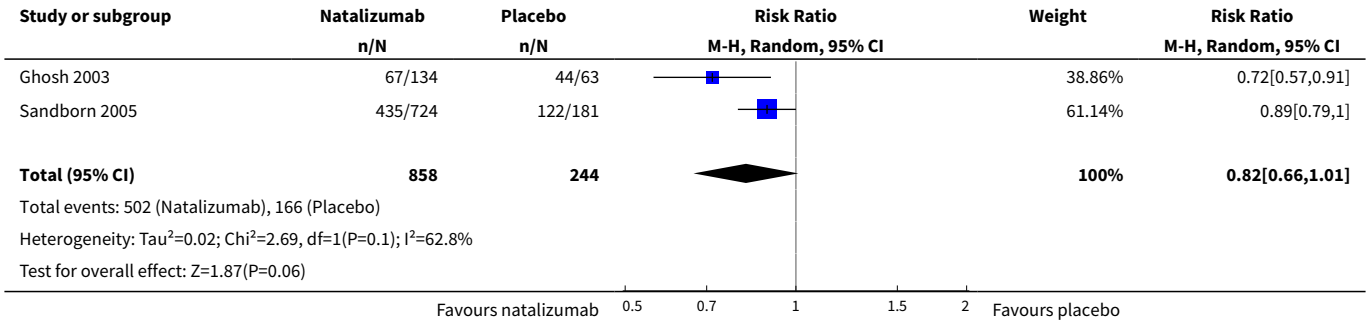
Analysis 1.2. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 2 Failure to induce remission at 4 weeks.

Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ghosh 2003	94/134	54/63		14.06%	0.82[0.7,0.95]
Sandborn 2005	558/724	147/181		45.03%	0.95[0.88,1.03]

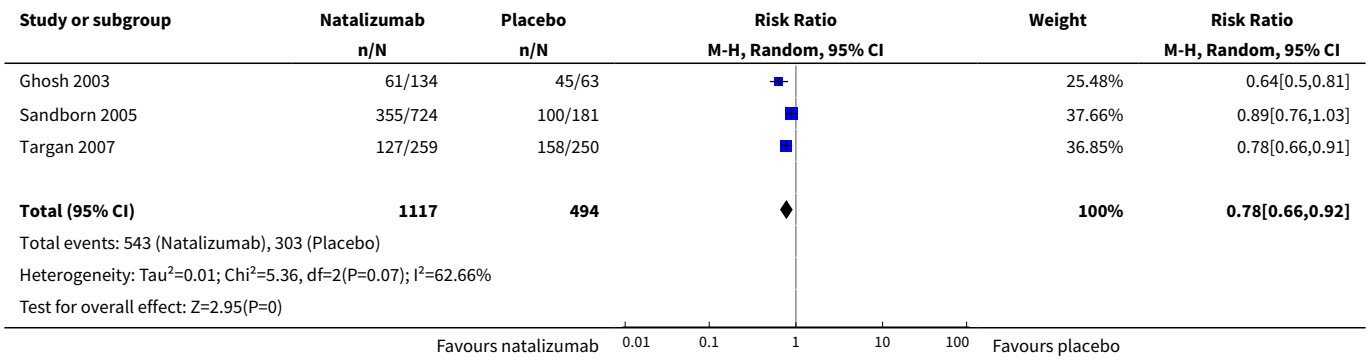




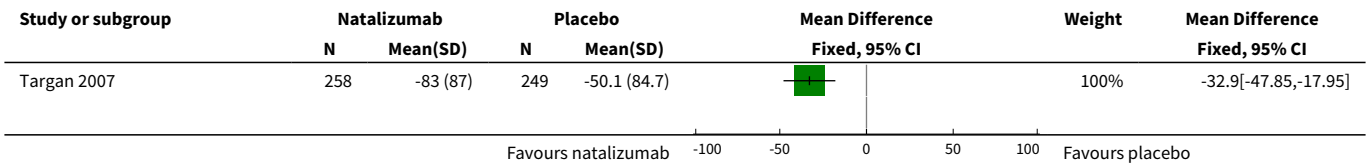
Analysis 1.3. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 3 Failure to induce clinical response at 2 weeks.

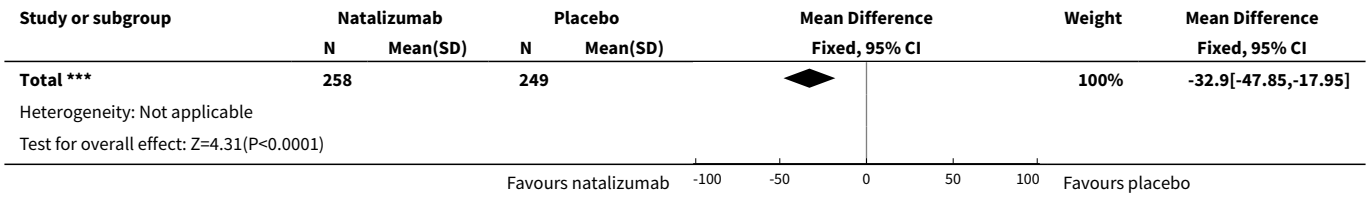


Analysis 1.4. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 4 Failure to induce clinical response at 4 weeks.

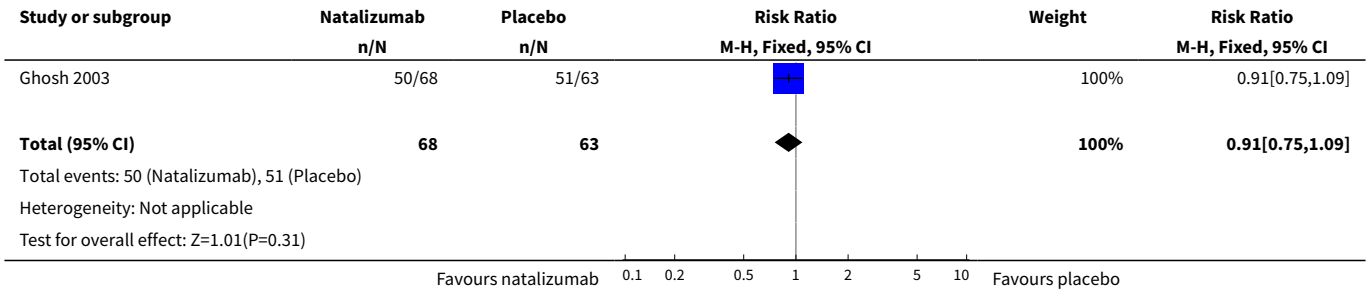


Analysis 1.5. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 5 Change in CDAI from baseline to 4 weeks.

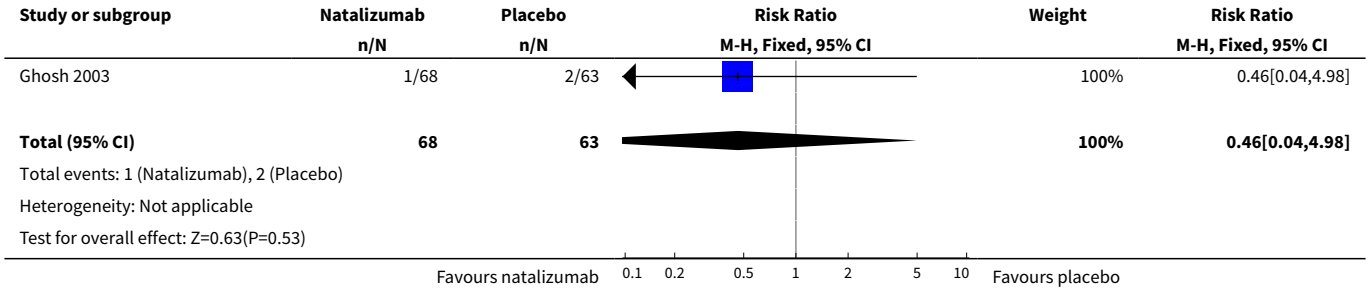




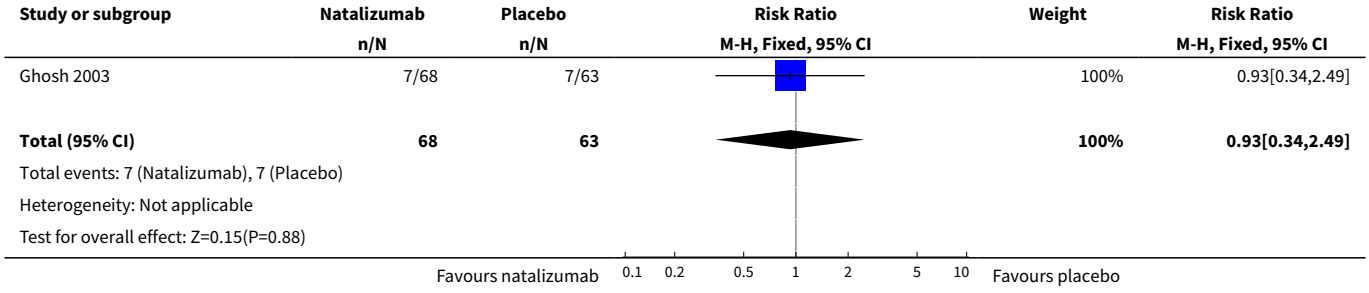
Analysis 1.6. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 6 Adverse events.



Analysis 1.7. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 7 Withdrawal due to adverse events.



Analysis 1.8. Comparison 1 One infusion of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 8 Serious adverse events up to week 12.

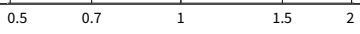


Comparison 2. Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce remission at 6 weeks	2	1034	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.78, 0.93]
2 Failure to induce remission at 8 weeks	3	1543	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.95]
3 Failure to induce clinical response at 6 weeks	2	1034	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.35, 1.25]
4 Faliure to induce clinical response at 8 weeks	3	1543	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.58, 0.91]
5 Change in CDAI from baseline to 8 weeks	1	507	Mean Difference (IV, Fixed, 95% CI)	-38.60 [-55.26, -21.94]
6 Adverse events	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.24]
7 Withdrawal due to adverse events	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.14, 6.57]
8 Serious adverse events up to week 12	1	129	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.29, 2.30]

Analysis 2.1. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 1 Failure to induce remission at 6 weeks.

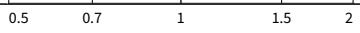
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ghosh 2003	37/66	46/63		17.36%	0.77[0.59,1]
Sandborn 2005	486/724	140/181		82.64%	0.87[0.79,0.95]
Total (95% CI)	**790**	**244**		**100%**	**0.85[0.78,0.93]**
Total events: 523 (Natalizumab), 186 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=3.55(P=0)					



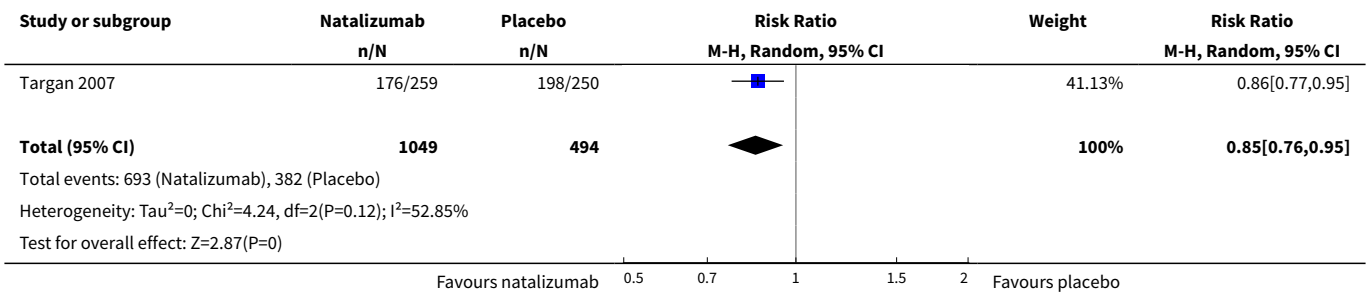
Favours natalizumab — Favours placebo

Analysis 2.2. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 2 Failure to induce remission at 8 weeks.

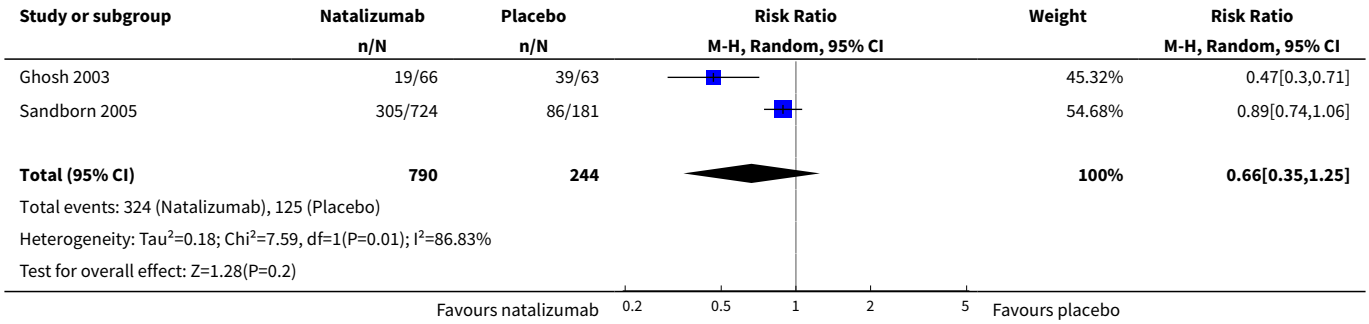
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ghosh 2003	39/66	53/63		17.46%	0.7[0.56,0.88]
Sandborn 2005	478/724	131/181		41.41%	0.91[0.82,1.01]



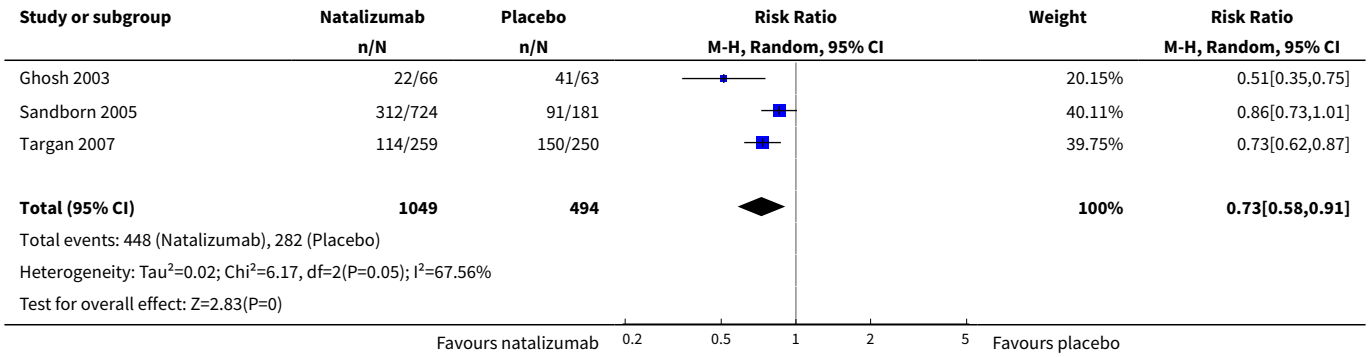
Favours natalizumab — Favours placebo



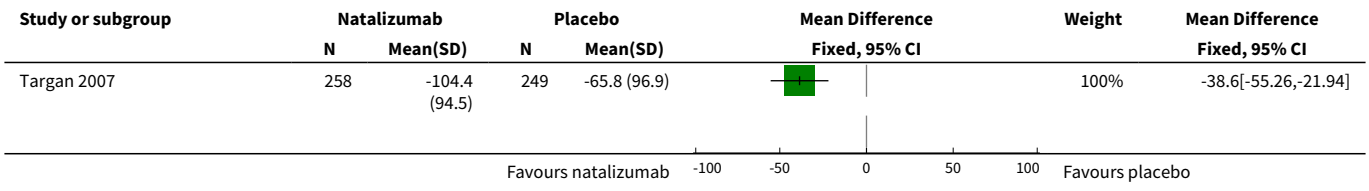
Analysis 2.3. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 3 Failure to induce clinical response at 6 weeks.

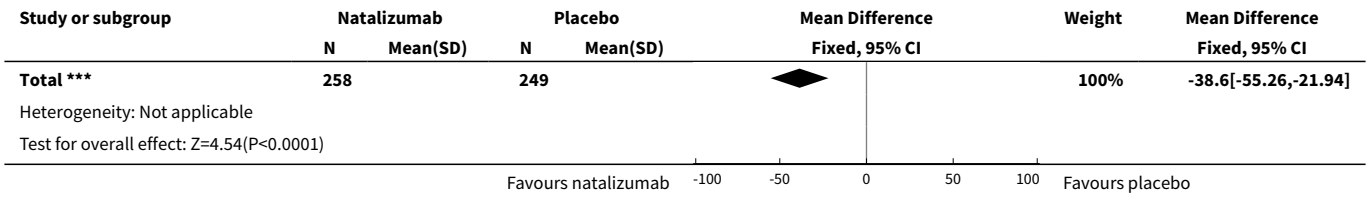


Analysis 2.4. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 4 Faliure to induce clinical response at 8 weeks.

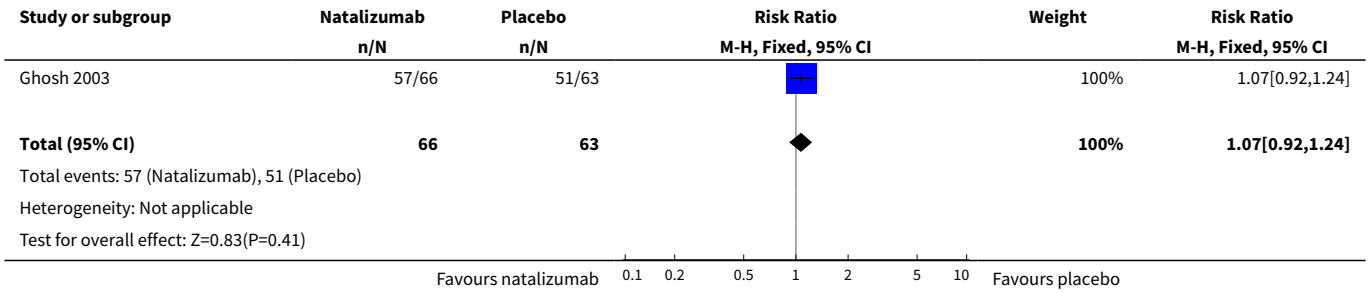


Analysis 2.5. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 5 Change in CDAI from baseline to 8 weeks.

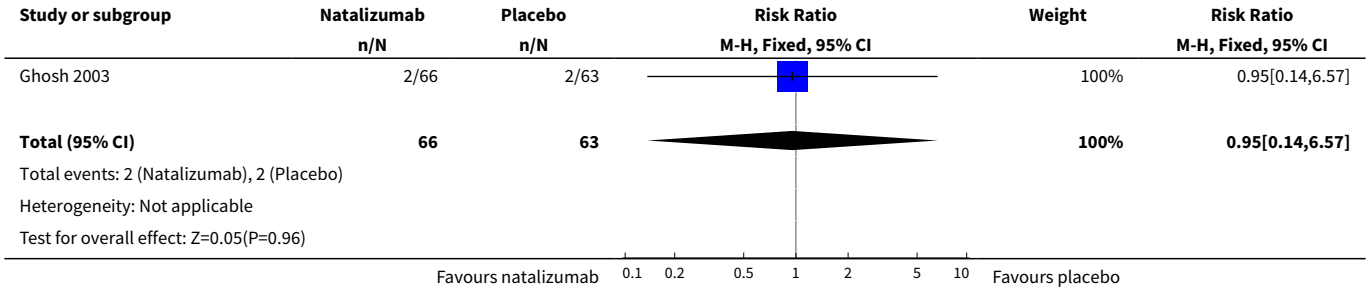




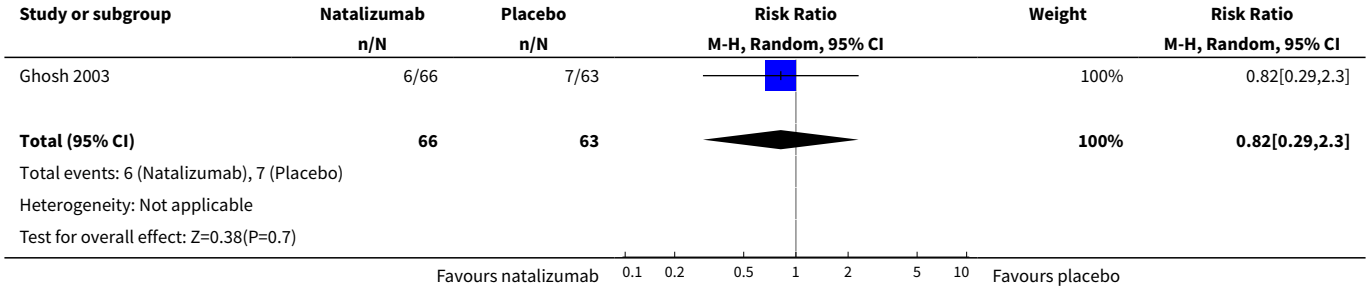
Analysis 2.6. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 6 Adverse events.



Analysis 2.7. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 7 Withdrawal due to adverse events.



Analysis 2.8. Comparison 2 Two infusions of natalizumab (300 mg or 3 mg/kg) versus placebo, Outcome 8 Serious adverse events up to week 12.



Comparison 3. Two infusions of natalizumab (6 mg/kg) versus placebo

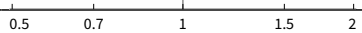
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce remission at 6 weeks	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.74, 1.19]
2 Failure to induce remission at 8 weeks	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.88]
3 Failure to induce clinical response at 6 weeks	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.01]
4 Failure to induce clinical response at 8 weeks	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.49, 0.99]
5 Adverse events	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
6 Withdrawal due to adverse events	1	114	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.32, 10.67]
7 Serious adverse events up to week 12	1	114	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.38, 2.95]

Analysis 3.1. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 1 Failure to induce remission at 6 weeks.

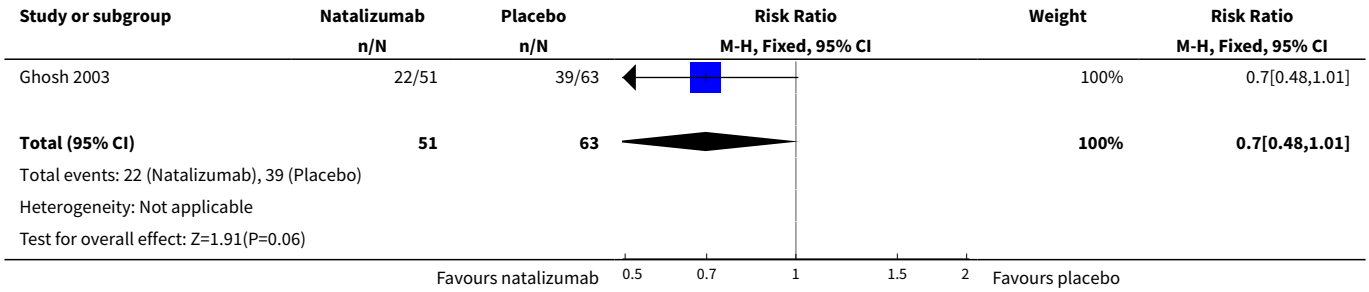
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ghosh 2003	35/51	46/63		100%	0.94[0.74,1.19]
Total (95% CI)	**51**	**63**		**100%**	**0.94[0.74,1.19]**
Total events: 35 (Natalizumab), 46 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					

Analysis 3.2. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 2 Failure to induce remission at 8 weeks.

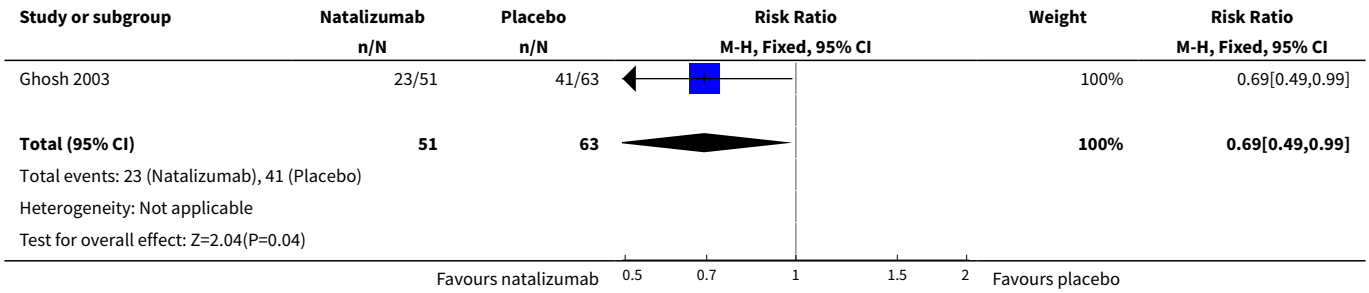
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ghosh 2003	29/51	53/63		100%	0.68[0.52,0.88]
Total (95% CI)	**51**	**63**		**100%**	**0.68[0.52,0.88]**
Total events: 29 (Natalizumab), 53 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.93(P=0)					



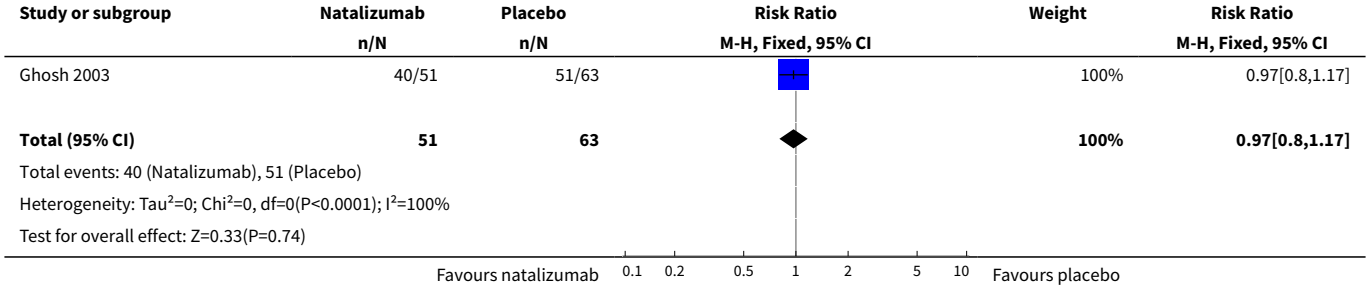
Analysis 3.3. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 3 Failure to induce clinical response at 6 weeks.



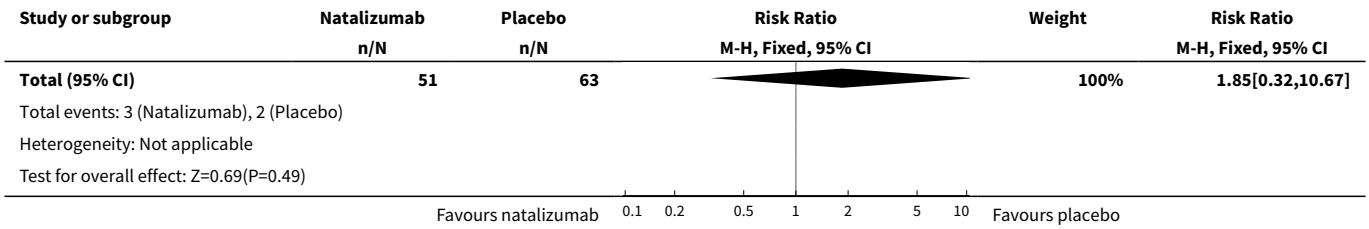
Analysis 3.4. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 4 Failure to induce clinical response at 8 weeks.



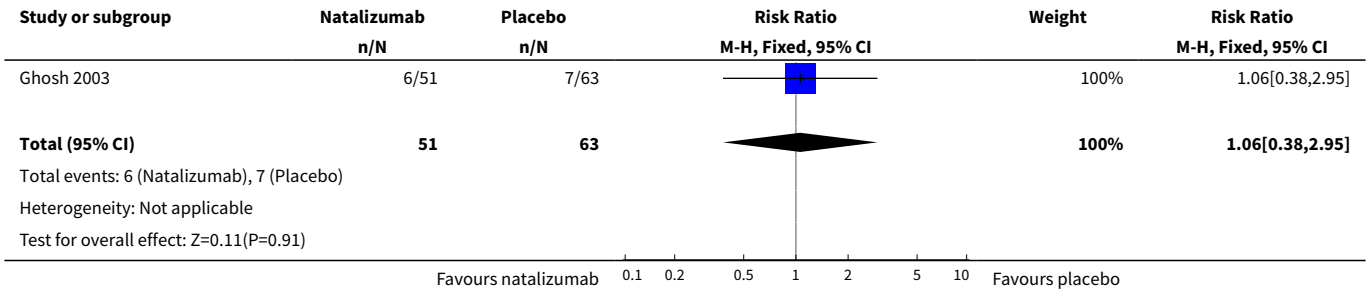
Analysis 3.5. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 5 Adverse events.



Analysis 3.6. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 6 Withdrawal due to adverse events.



Analysis 3.7. Comparison 3 Two infusions of natalizumab (6 mg/kg) versus placebo, Outcome 7 Serious adverse events up to week 12.



Comparison 4. Three infusions of natalizumab (300 mg) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce remission at 10 weeks	1	905	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.01]
2 Failure to induce remission at 12 weeks	2	1414	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.78, 0.92]
3 Failure to induce clinical response at 10 weeks	1	905	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.00]
4 Failure to induce clinical response at 12 weeks	2	1414	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.67, 0.86]
5 Change in CDAI from baseline to 12 weeks	1	507	Mean Difference (IV, Fixed, 95% CI)	-49.60 [-67.35, -31.85]
6 Adverse events up to week 12	2	1415	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.08]
7 Withdrawal due to adverse event	2	1415	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.26]
8 Serious adverse events	2	1414	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.37, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Failure to induce remission at 10 weeks (post hoc subgroup analyses)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Patients with elevated CRP at baseline	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.73, 0.94]
9.2 Concurrent use of immunosuppressants	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.67, 0.96]
9.3 Previous use of anti-TNF therapy	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.98]
10 Failure to induce remission at 12 weeks (post hoc subgroup analyses)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Patients with elevated CRP at baseline	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.71, 0.92]
10.2 Concurrent use of immunosuppressants	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.96]
10.3 Previous use of anti-TNF therapy	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.98]
11 Failure to induce clinical response at 10 weeks (post hoc subgroup analyses)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Patients with elevated CRP at baseline	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.63, 0.91]
11.2 Concurrent use of immunosuppressants	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.51, 0.89]
11.3 Previous use of anti-TNF therapy	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.55, 0.84]
12 Failure to induce clinical response at 12 weeks (post hoc subgroup analyses)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Patients with elevated CRP at baseline	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.58, 0.86]
12.2 Concurrent use of immunosuppressants	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.91]
12.3 Previous use of anti-TNF therapy	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.53, 0.83]

Analysis 4.1. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 1 Failure to induce remission at 10 weeks.

Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2005	457/724	126/181		100%	0.91[0.81,1.01]
Total (95% CI)	**724**	**181**		**100%**	**0.91[0.81,1.01]**
Total events: 457 (Natalizumab), 126 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.73(P=0.08)					

Favours natalizumab — Favours placebo

Analysis 4.2. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 2 Failure to induce remission at 12 weeks.

Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2005	435/724	125/181		51.11%	0.87[0.78,0.98]
Targan 2007	161/259	188/250		48.89%	0.83[0.73,0.93]
Total (95% CI)	**983**	**431**		**100%**	**0.85[0.78,0.92]**
Total events: 596 (Natalizumab), 313 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=3.9(P<0.0001)					

Favours placebo — Favours natalizumab

Analysis 4.3. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 3 Failure to induce clinical response at 10 weeks.

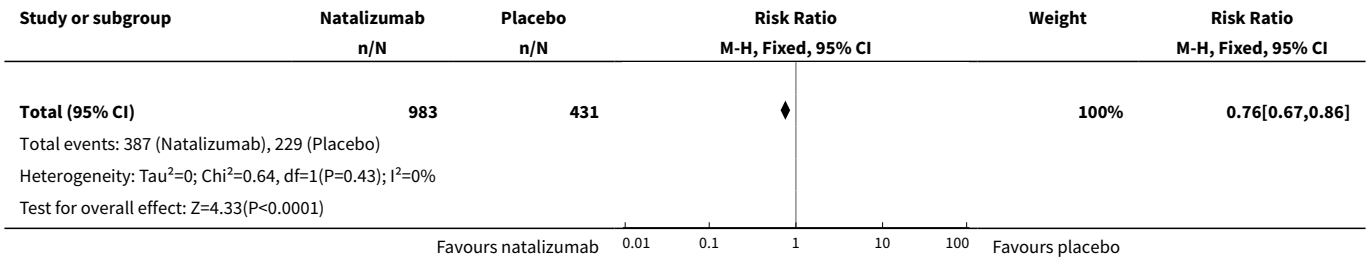
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2005	316/724	93/181		100%	0.85[0.72,1]
Total (95% CI)	**724**	**181**		**100%**	**0.85[0.72,1]**
Total events: 316 (Natalizumab), 93 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					

Favours natalizumab — Favours placebo

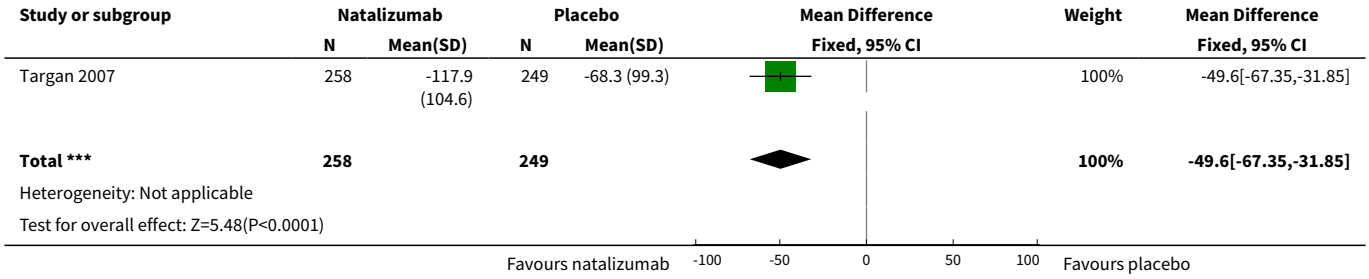
Analysis 4.4. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 4 Failure to induce clinical response at 12 weeks.

Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2005	283/724	89/181		49.99%	0.79[0.67,0.95]
Targan 2007	104/259	140/250		50.01%	0.72[0.6,0.86]

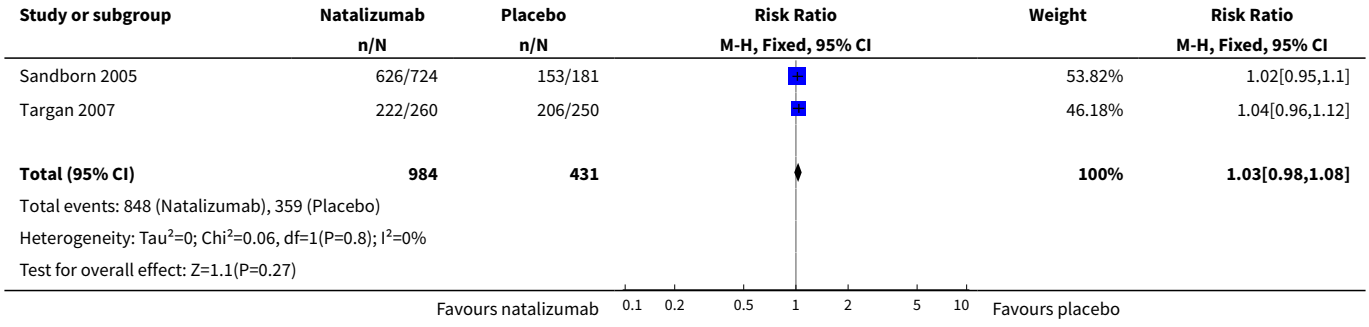
Favours natalizumab — Favours placebo



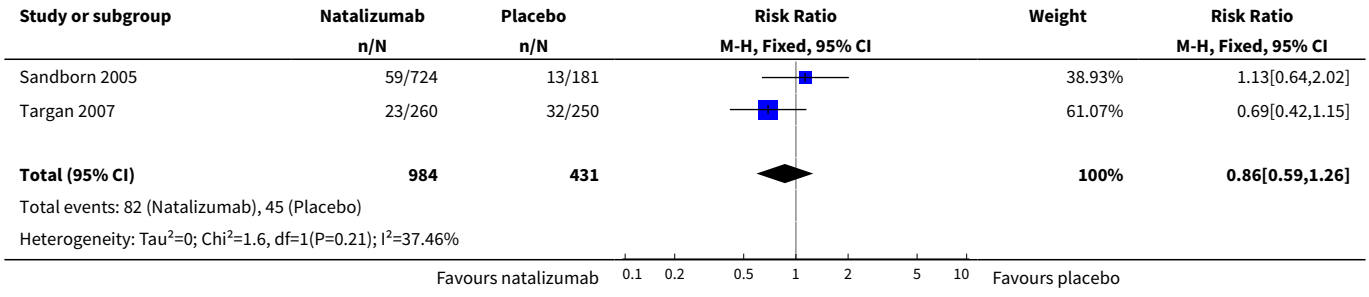
Analysis 4.5. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 5 Change in CDAI from baseline to 12 weeks.



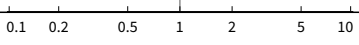
Analysis 4.6. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 6 Adverse events up to week 12.



Analysis 4.7. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 7 Withdrawal due to adverse event.



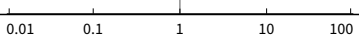
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.76(P=0.45)					



Favours natalizumab | Favours placebo

Analysis 4.8. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 8 Serious adverse events.

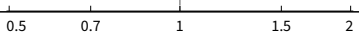
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sandborn 2005	52/723	12/181		51.4%	1.08[0.59,1.99]
Targan 2007	13/260	24/250		48.6%	0.52[0.27,1]
Total (95% CI)	**983**	**431**		**100%**	**0.76[0.37,1.56]**
Total events: 65 (Natalizumab), 36 (Placebo)					
Heterogeneity: Tau^2=0.17; Chi^2=2.61, df=1(P=0.11); I^2=61.67%					
Test for overall effect: Z=0.75(P=0.45)					



Favours experimental | Favours control

Analysis 4.9. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 9 Failure to induce remission at 10 weeks (post hoc subgroup analyses).

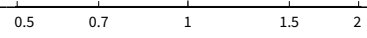
Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.9.1 Patients with elevated CRP at baseline					
Sandborn 2005	316/526	97/134		100%	0.83[0.73,0.94]
Subtotal (95% CI)	**526**	**134**		**100%**	**0.83[0.73,0.94]**
Total events: 316 (Natalizumab), 97 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.91(P=0)					
4.9.2 Concurrent use of immunosuppressants					
Sandborn 2005	149/247	40/53		100%	0.8[0.67,0.96]
Subtotal (95% CI)	**247**	**53**		**100%**	**0.8[0.67,0.96]**
Total events: 149 (Natalizumab), 40 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.39(P=0.02)					
4.9.3 Previous use of anti-TNF therapy					
Sandborn 2005	195/290	54/68		100%	0.85[0.73,0.98]
Subtotal (95% CI)	**290**	**68**		**100%**	**0.85[0.73,0.98]**
Total events: 195 (Natalizumab), 54 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.24(P=0.02)					



Favours natalizumab | Favours placebo

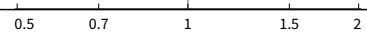
Analysis 4.10. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 10 Failure to induce remission at 12 weeks (post hoc subgroup analyses).

Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.10.1 Patients with elevated CRP at baseline					
Sandborn 2005	306/526	96/134		100%	0.81[0.71,0.92]
Subtotal (95% CI)	**526**	**134**		**100%**	**0.81[0.71,0.92]**
Total events: 306 (Natalizumab), 96 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.17(P=0)					
4.10.2 Concurrent use of immunosuppressants					
Sandborn 2005	144/247	39/53		100%	0.79[0.65,0.96]
Subtotal (95% CI)	**247**	**53**		**100%**	**0.79[0.65,0.96]**
Total events: 144 (Natalizumab), 39 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.37(P=0.02)					
4.10.3 Previous use of anti-TNF therapy					
Sandborn 2005	195/290	54/68		100%	0.85[0.73,0.98]
Subtotal (95% CI)	**290**	**68**		**100%**	**0.85[0.73,0.98]**
Total events: 195 (Natalizumab), 54 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.24(P=0.02)					

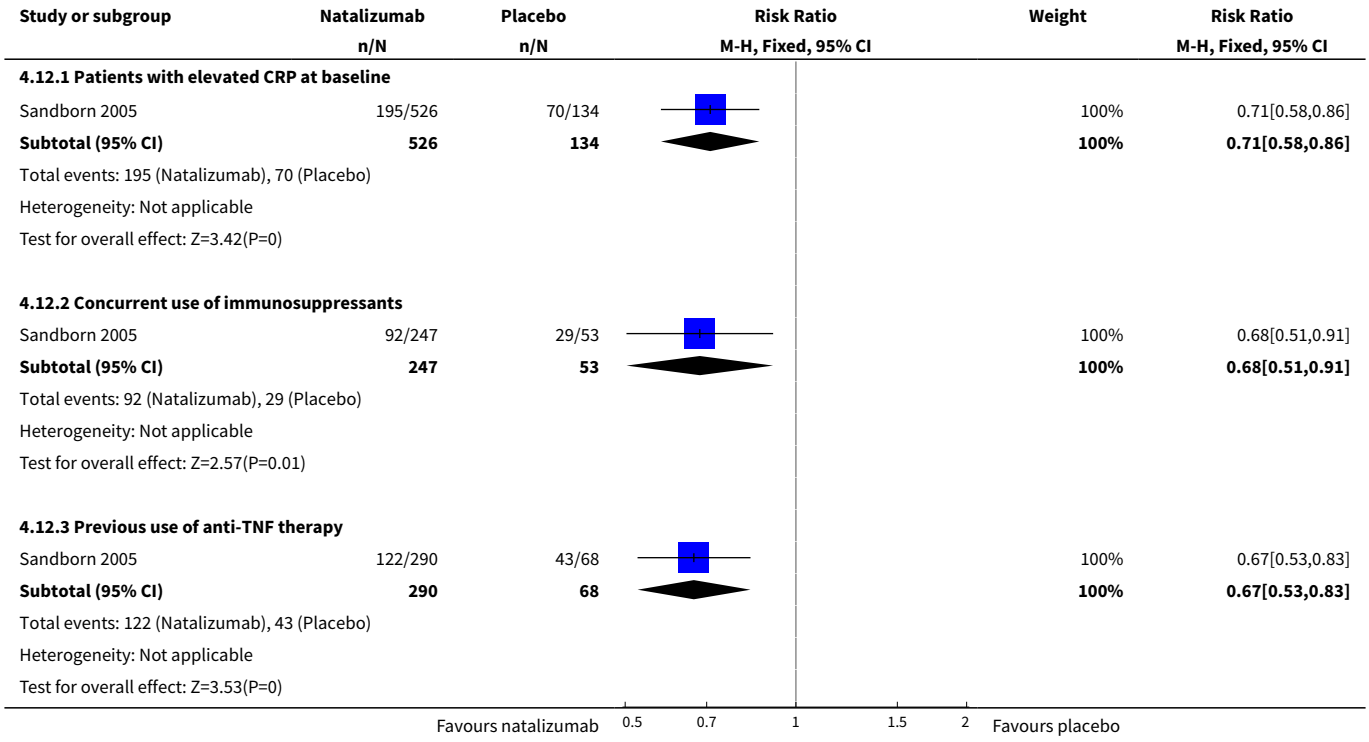


Analysis 4.11. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 11 Failure to induce clinical response at 10 weeks (post hoc subgroup analyses).

Study or subgroup	Natalizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.11.1 Patients with elevated CRP at baseline					
Sandborn 2005	221/526	74/134		100%	0.76[0.63,0.91]
Subtotal (95% CI)	**526**	**134**		**100%**	**0.76[0.63,0.91]**
Total events: 221 (Natalizumab), 74 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.94(P=0)					
4.11.2 Concurrent use of immunosuppressants					
Sandborn 2005	94/247	30/53		100%	0.67[0.51,0.89]
Subtotal (95% CI)	**247**	**53**		**100%**	**0.67[0.51,0.89]**
Total events: 94 (Natalizumab), 30 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.74(P=0.01)					
4.11.3 Previous use of anti-TNF therapy					
Sandborn 2005	131/290	45/68		100%	0.68[0.55,0.84]
Subtotal (95% CI)	**290**	**68**		**100%**	**0.68[0.55,0.84]**
Total events: 131 (Natalizumab), 45 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.53(P=0)					



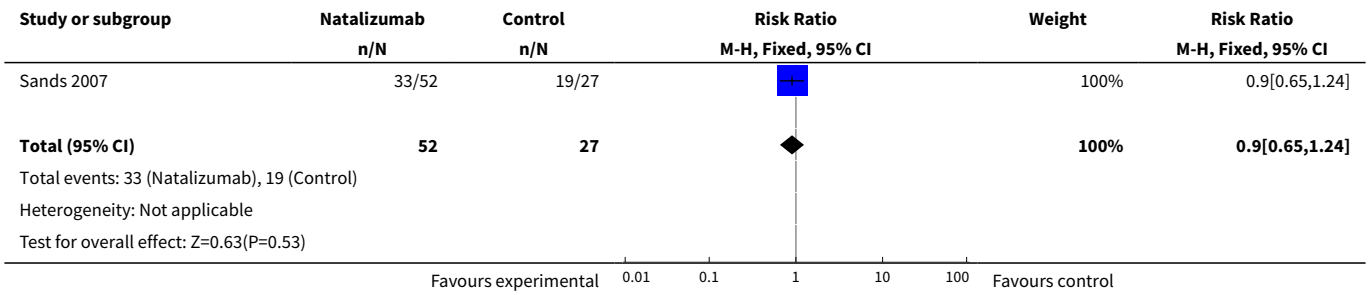
Analysis 4.12. Comparison 4 Three infusions of natalizumab (300 mg) versus placebo, Outcome 12 Failure to induce clinical response at 12 weeks (post hoc subgroup analyses).



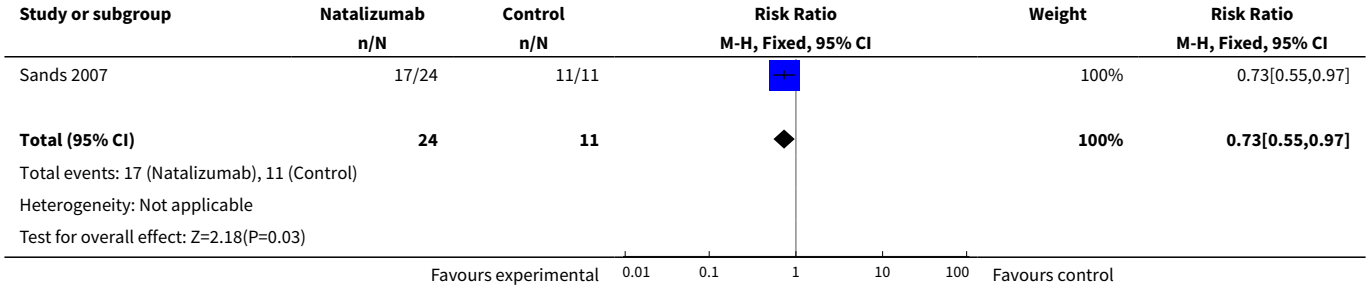
Comparison 5. Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce clinical remission at week 10	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.24]
2 Failure to induce remission at week 10 in patients with elevated CRP at baseline (posthoc subgroup analysis)	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.97]
3 Adverse events	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.85, 1.03]
4 Withdrawal due to adverse events	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.18]
5 Serious adverse events	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.03, 7.98]

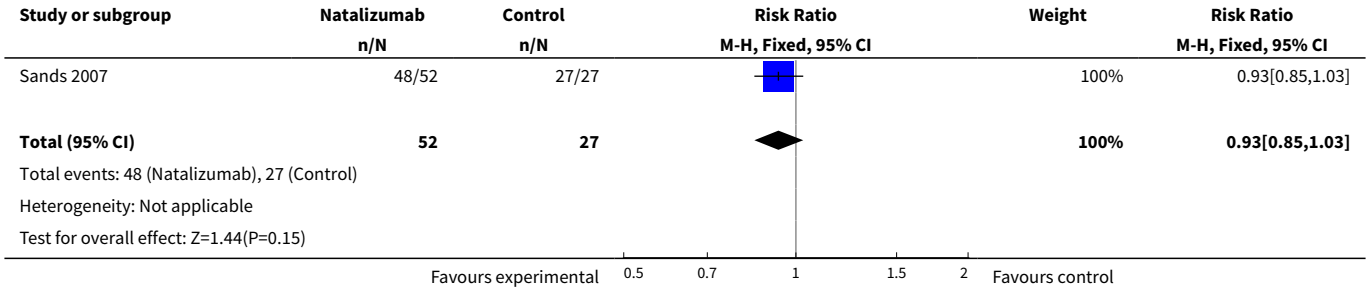
Analysis 5.1. Comparison 5 Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab, Outcome 1 Failure to induce clinical remission at week 10.



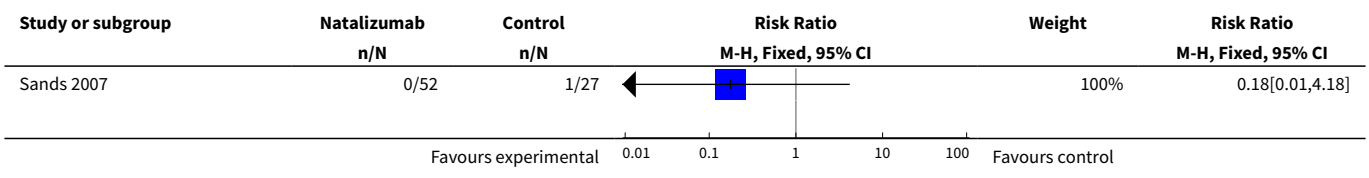
Analysis 5.2. Comparison 5 Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab, Outcome 2 Failure to induce remission at week 10 in patients with elevated CRP at baseline (posthoc subgroup analysis).

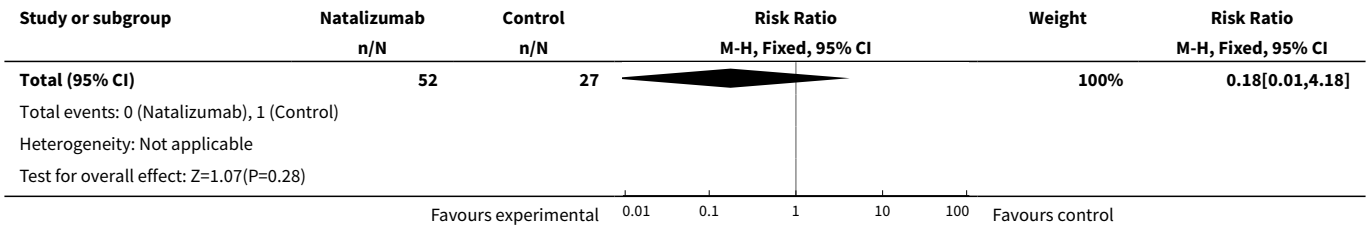


Analysis 5.3. Comparison 5 Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab, Outcome 3 Adverse events.

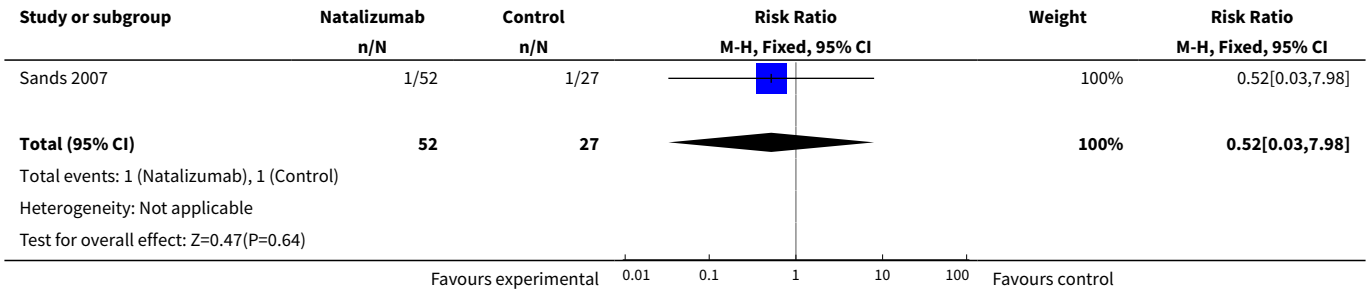


Analysis 5.4. Comparison 5 Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab, Outcome 4 Withdrawal due to adverse events.





Analysis 5.5. Comparison 5 Three infusions of natalizumab (300 mg) and two infusions of infliximab versus placebo and two infusions of infliximab, Outcome 5 Serious adverse events.



APPENDICES

Appendix 1. Electronic Search Strategy

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19. crohn.mp. or exp Crohn disease/

20. (inflammatory bowel disease* or IBD).mp.

21. 19 or 20

22. 18 and 21

23. Natalizumab.mp.

24. Antegren.mp.

25. Tysabri.mp.

26. Antibodies, Monoclonal.mp. or exp antibodies, monoclonal/

27. 23 or 24 or 25 or 26

28. 22 and 27

EMBASE

1. random$.tw.

2. factorial$.tw.

3. (crossover$ or cross over$ or cross-over$).tw.

4. placebo$.tw.

5. single blind.mp.

6. double blind.mp.

7. triple blind.mp.

8. (singl$ adj blind$).tw.

9. (double$ adj blind$).tw.

10. (tripl$ adj blind$).tw.

11. assign$.tw.

12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19. crohn.mp. or exp Crohn disease/

20. (inflammatory bowel disease* or IBD).mp.

21. 19 or 20

22. 18 and 21

23. Natalizumab.mp.

24. Antegren.mp.

25. Tysabri.mp.

26. Antibodies, Monoclonal.mp. or exp antibodies, monoclonal/

27. 23 or 24 or 25 or 26

28. 22 and 27

Cochrane Library

#1. crohn* OR IBD OR "inflammatory bowel disease*"

#2. Natalizumab or Antegren or Tysabri or monoclonal antibodies

#3. #1 and #2

SR-IBD

Natalizumab or Antegren or Tysabri or monoclonal antibodies

Clinicaltrials.gov

Natalizumab and Crohns Disease

WHAT'S NEW

Date	Event	Description
10 May 2018	New citation required and conclusions have changed	Updated review with changes to the conclusions and new authors
10 May 2018	New search has been performed	New literature search was run on 10 May 2018. One new study was added to the review

DECLARATIONS OF INTEREST

Seana ML Nelson: None known

Tran M Nguyen: None known

John WD McDonald: None known

John K MacDonald: None known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review update includes a PRISMA flow diagram, a risk of bias assessment of included studies (to replace the Jadad scale), a GRADE analysis and Summary of Findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [administration & dosage] [*therapeutic use]; Antibodies, Monoclonal, Humanized; Crohn Disease [*drug therapy]; Gastrointestinal Agents [administration & dosage] [therapeutic use]; Immunologic Factors [administration & dosage] [adverse effects] [*therapeutic use]; Induction Chemotherapy; Infliximab [administration & dosage] [therapeutic use]; Integrin

alpha4; Integrins [antagonists & inhibitors]; Natalizumab [administration & dosage] [adverse effects] [*therapeutic use]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Treatment Failure

MeSH check words

Humans