Natalizumab increased clinical remission and clinical response in moderate-to-severe Crohn disease

Ghosh S, Goldin E, Gordon FH, et al. **Natalizumab for active Crohn's disease.** N Engl J Med. 2003;348:24-32.

QUESTION

In patients with moderate-to-severe Crohn disease, is natalizumab (NZB) more effective than placebo for inducing clinical remission and clinical response?

DESIGN

Randomized {allocation concealed*}†, blinded (clinicians and patients),* placebo-controlled trial with 12-week follow-up (Natalizumab Pan-European Study).

SETTING

35 study centers in Belgium, the Czech Republic, Denmark, Germany, Israel, the Netherlands, Sweden, and the United Kingdom.

PATIENTS

248 patients ≥ 18 years of age (mean age 35 y, 55% women) who had clinical evidence of moderate-to-severe Crohn disease (defined as Crohn's Disease Activity Index [CDAI] score 220 to 450). Exclusion criteria included use of methotrexate or cyclosporine ≤ 3 months before randomization, current use of systemic corticosteroids at daily dose equivalents > 25 mg of oral prednisolone, and previous treatment with any antibody agent. Follow-up was 88%.

INTERVENTION

Patients were allocated to 1 of 4 groups: 2 infusions of NZB, 6 mg/kg of body weight (NZB6 group, $n = 51$); 2 infusions of NZB, 3 mg/kg (NZB3 group, $n = 66$); 1 infusion of NZB, 3 mg/kg, and 1 infusion of placebo ($n = 68$); or 2 infusions of placebo ($n = 63$). The infusions were administered intravenously 4 weeks apart.

MAIN OUTCOME MEASURES

CDAI score measured at week 2, 4, 6, 8, and 12, with subsequent classification of patients as having clinical remission (CDAI score < 150) or clinical response (decrease from baseline in CDAI score of ≥ 70).

MAIN RESULTS

Analysis was by intention to treat. At 6 weeks, the NZB6 group did not differ from the placebo group for rate of clinical remission (primary endpoint in the efficacy analysis) (Table). However, the NZB6 group had greater rates of clinical remission than the placebo group at 4 and 8 weeks (P values < 0.05). At week 4, all NZB groups had greater rates of clinical remission than the placebo group (P values < 0.05). The NZB3 group had greater rates of remission than placebo at weeks 6 (Table), 8, and 12 (P values < 0.05). The rates of clinical response were greater in all 3 NZB groups than in the placebo group at weeks 4, 6 (Table), and 8 (P values < 0.05).

CONCLUSION

In patients with moderate-to-severe Crohn disease, natalizumab was more effective than placebo for increasing the rates of clinical remission and clinical response.

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*See Glossary.

†Information provided by author.

2 infusions of natalizumab (NZB), 6 mg/kg (NZB6); 2 infusions of NZB, 3 mg/kg (NZB3); or 1 infusion of NZB, 3 mg/kg, and 1 infusion of placebo (NZB3-P) vs 2 infusions of placebo at 6 weeks‡

Outcomes	Comparison	Event rates	RBI (95% CI)	NNT (CI)
Clinical remission	NZB6 vs placebo	31% vs 27%	16% (–34 to 105)	Not significant
	NZB3 vs placebo	44% vs 27%	63% (1 to 168)	6 (4 to 280)
	NZB3-P vs placebo	29% vs 27%	9% (–37 to 88)	Not significant
Clinical response	NZB6 vs placebo	57% vs 38%	49% (1 to 123)	6 (3 to 368)
	NZB3 vs placebo	71% vs 38%	87% (34 to 170)	4 (3 to 7)
	NZB3-P vs placebo	59% vs 38%	54% (8 to 127)	5 (3 to 29)

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

NZB, a humanized monoclonal antibody against α_4-integrin, seems to be effective treatment for active Crohn disease by inhibiting migration, activation, or survival of lymphocytes homing to the intestine. The trial by Ghosh and colleagues provides compelling evidence that NZB should join our armamentarium of new biologicals.

Like other biological drugs, the effective dosing window may be quite narrow and supports 2 infusions of 3 mg/kg 4 weeks apart, with little apparent added benefit for 6-mg/kg infusions. The peak efficacy for all outcomes (remission, response, improved quality of life, and levels of C-reactive protein) occurred at 6 weeks, as anticipated by the study design. However, benefit occurred as early as 2 weeks and was sustained at 12 weeks for some outcomes. In general, rates of remission (29% to 44%) and response (57% to 71%) were similar to those observed in trials of infliximab (1). However, no data were presented addressing whether patients taking corticosteroids or an immunosuppressive (6-mercaptopurine or azathioprine) were more or less likely to benefit.

Whereas the treatment effects might be slightly more durable than for infliximab, this observation will need to be the primary question of a long-term follow-up trial. Note should be made of the relatively high placebo response rates—remission 27% and response 38%, perhaps partly reflecting the statistical technique of last value carried forward. The smaller size of the NZB6 group ($n = 51$) and its overrepresentation of fistulizing disease (no data provided whether perianal or abdominal) might have contributed to the observed lack of "dose response." Careful correlation of circulating lymphocyte, leukocyte levels, and other potential predictors of response should be examined in future studies.

The adverse event rates seemed to be acceptable. In particular, infections did not appear to be increased in the NZB groups. However, longer follow-up with repeated infusions is needed. Similarly, only 2 infusion reactions occurred, both after second infusions and one in a patient who developed binding antibodies to NZB. It was not mentioned whether antinuclear antibody titers were assessed at baseline or if these patients were taking corticosteroids. As with other biological agents, careful observation for serum sickness syndromes and opportunistic infections, such as tuberculosis, will be essential.

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Reference

1. Crohn's Disease cA2 Study Group. N Engl J Med. 1997;337:1029-35.