

Maintenance infliximab delayed loss of response in active Crohn disease

Hanauer SB, Feagan BG, Lichtenstein GR, et al., and the ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002 May 4;359:1541-9.

QUESTION

In patients with active Crohn disease who have responded to a single infusion of infliximab within 2 weeks, is maintenance treatment with infliximab more effective than placebo for delaying loss of response?

DESIGN

54-week, randomized (allocation concealed*), blinded (clinicians and patients)*, placebo-controlled trial.

SETTING

North America (40 sites), Europe (13 sites), and Israel (2 sites).

PATIENTS

335 of 573 patients (median age 35 y, 61% women) who had Crohn disease \geq 3 months in duration; had a Crohn's Disease Activity Index (CDAI) score between 220 and 400; and responded to a single infusion of infliximab, 5 mg/kg, within 2 weeks. Response was defined as a decrease in CDAI score \geq 70 points from baseline and a reduction in the total score \geq 25%. Exclusion criteria included previous treatment with infliximab or any other agent targeted at tumor-necrosis factor. Follow-up was 100%.

INTERVENTION

Patients were allocated to a maintenance regimen of infliximab, 10 mg/kg ($n = 112$); infliximab, 5 mg/kg ($n = 113$); or placebo ($n = 110$). At weeks 2 and 6, patients received maintenance infusions of infliximab, 5 mg/kg (infliximab groups), or placebo. After week 6, each group received the corresponding regimen every 8 weeks until week 46.

MAIN OUTCOME MEASURES

Clinical remission (CDAI $<$ 150) at week 30 and time to loss of response up to week 54.

MAIN RESULTS

Analysis was by intention to treat. At 30 weeks, more patients were still in clinical remission in both of the infliximab groups

than in the placebo group (Table). At 54 weeks, time to loss of response was greater in both of the infliximab groups than in the placebo group (Table).

CONCLUSION

In patients with active Crohn disease who have responded to a single infusion of infliximab within 2 weeks, maintenance treatment with infliximab was more effective than placebo for delaying loss of response.

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*See Glossary.

Infliximab 10 mg/kg (IFB10) or 5 mg (IFB5) vs placebo for maintenance therapy of Crohn disease†

Outcomes	Comparison	Event rates	RBI (95% CI)	NNT (CI)
Clinical remission at 30 wk	IFB10 vs placebo	45% vs 21%	114% (42 to 226)	5 (3 to 9)
	IFB5 vs placebo	39% vs 21%	86% (22 to 187)	6 (4 to 17)
		Medians	P value	
Time to loss of response (wk) at 54 wk	IFB10 vs placebo	> 54 vs 19	< 0.001	
	IFB5 vs placebo	38 vs 19	0.002	

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

COMMENTARY

Infliximab, a chimeric human–murine monoclonal antibody against tumor-necrosis factor- α , was launched in 1998. Helped by dramatic photographs of endoscopic healing, it has become widely used for difficult Crohn disease, with > 140 000 patients having received it worldwide. 2 infusions may be given initially for inflammatory disease and 3 when fistulas are present. Infliximab can induce remission in about 33% of patients who do not respond to standard treatment, but most relapse, often rapidly (1). In addition, this treatment is expensive (\$2500 per infusion), and some concerns exist about long-term safety, particularly in patients with tuberculosis, demyelination, and cancer (2). Thus, important questions remain: Is it a first-, second-, or third-line treatment? If combined with immunosuppressive medication, will it produce sustained remissions? Does ACCENT I by Hanauer and colleagues provide any answers?

Only patients who responded to a single infusion were enrolled, thereby favoring responders. Despite this bias, the 1-year "remission" rate was < 40%. How this score-defined remission relates to clinical practice is unclear because the number of patients who stopped the study treatment was similar across the 3 groups; the rates of stopping for lack of efficacy were 8% in the overall infliximab group and only

12% in the placebo group. The trial lasted 54 weeks; therefore, data on response past this point are not available. Finally, only 25% of patients recruited were receiving immunosuppressive medications, which are now standard treatment for all but the mildest conditions; immunosuppressive status (naïve or intolerant) for the remaining patients was not reported.

While ACCENT I shows that repeated infliximab infusions can maintain Crohn disease remission and are relatively safe in the short term, those looking for guidance on its use in achieving prolonged remission or its use in combination with immunosuppressive medication will be disappointed.

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References

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2. van Deventer SJ. Anti-tumour necrosis factor therapy in Crohn's disease: where are we now? *Gut*. 2002;51:362-3.