Infliximab at different doses was effective for rheumatoid arthritis after unsuccessful methotrexate treatment

Maini R, St. Clair EW, Breedveld F, et al., for the ATTRACT Study Group. **Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial.** Lancet. 1999 Dec 4; 354:1932-9.

QUESTION

Is infliximab safe and effective for relieving signs and symptoms in patients who have rheumatoid arthritis (RA) and do not respond to methotrexate?

DESIGN

Randomized (allocation concealed*), blinded (investigators and patients),* placebo-controlled trial with 30-week follow-up.

SETTING

34 centers in North America and Europe.

PATIENTS

428 patients who were 19 to 78 years of age (median age range for groups 51 to 56 y, 78% women); had a diagnosis of RA according to the 1987 American College of Rheumatology (ACR) criteria with evidence of active disease after treatment with methotrexate for ≥ 3 months; had received stable doses of methotrexate, ≥ 12.5 mg/wk, and folic acid for ≥ 4 weeks before screening; and had hemoglobin levels ≥ 5.3 mmol/L, white blood cell counts ≥ 3.5 × 10^9/L, a neutrophil count of 1.5 × 10^6/L, platelet counts ≥ 100 × 10^9/L, and normal liver and renal function. Patients who received oral corticosteroids were included if their dose had been stable for ≥ 4 weeks. Exclusion criteria included current inflammatory conditions, use of drugs other than methotrexate for RA, known allergy to murine proteins, previous or recent infections, or serious medical conditions. 81% of patients completed the study.

INTERVENTION

Patients were allocated for 30 weeks to intravenous infusions of infliximab, 3 mg/kg of body weight every 8 weeks (n = 86), 3 mg/kg every 4 weeks (n = 86), 10 mg/kg every 8 weeks (n = 87), or 10 mg/kg every 4 weeks (n = 81), or to placebo (n = 88).

MAIN OUTCOME MEASURE

Response rate at week 30 (defined as 20% improvement from baseline according to ACR criteria).

MAIN RESULTS

More patients in the infliximab groups than in the placebo group had a 20% improvement ($P < 0.001$) (Table). Serious adverse effects did not differ among groups. Infection occurred more frequently in the 10-mg infliximab groups (64% in 8-week group, 73% in 4-week group) than in the placebo group (40%, $P \leq 0.001$).

CONCLUSION

In patients who have rheumatoid arthritis and did not respond to methotrexate, infliximab was effective for relieving signs and symptoms.

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*See Glossary.

Response rates (defined as 20% improvement) at 30 weeks for infliximab vs placebo in rheumatoid arthritis after unsuccessful methotrexate treatment†

Infliximab regimen	Infliximab	Placebo	RBI (95% CI)	NNT (CI)
3 mg/kg every 4 wk	53%	20%	161% (68 to 316)	4 (3 to 6)
3 mg/kg every 8 wk	50%	20%	144% (56 to 291)	4 (3 to 7)
10 mg/kg every 4 wk	58%	20%	184% (84 to 350)	3 (2 to 5)
10 mg/kg every 8 wk	52%	20%	153% (62 to 304)	4 (3 to 6)

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

COMMENTARY

The study by Maini and colleagues shows that antitumor necrosis factor α (TNF-α) blockade (infliximab) acts synergistically with methotrexate to suppress the acute-phase response and to reduce rheumatoid synovitis. However, 50% improvement was achieved in only 26% to 31% of patients in the treatment groups in a 30-week trial. Thus, it is important to identify the patients most likely to benefit from this expensive treatment. The disease duration ranged from 7.2 to 9.0 years, and 18% to 29% of patients had already had joint surgery. Earlier treatment with TNF-α blockade might prove more effective.

The long-term safety of TNF-α blockade is of concern. The incidence of infection was higher in the treatment groups, and the authors reported that such infections may be serious for some patients in the longer term. The relative merits of new antirheumatic agents must also be considered. Etanercept has proved to be as effective and well tolerated as infliximab in suppressing both the acute-phase response and synovitis in short-term trials (1). It is given subcutaneously but is used more frequently than infliximab. Unlike infliximab, etanercept does not induce antibodies to the drug. However, it is also expensive. Leflunomide substantially suppresses both the acute-phase response and synovitis. Diarrhea is the main side effect (2). Leflunomide is given orally and is far less expensive than infliximab or etanercept. Furthermore, it improves patients' health-related quality-of-life scores (3).

These new agents offer a realistic prospect of more effective treatment for RA. Their efficacy, relative merits, and indications for use can only be established in long-term studies that address the stage at which they should be introduced, their ability to suppress joint erosion, safety issues, and cost-effectiveness. Currently, leflunomide is a simple alternative to methotrexate, whereas infliximab or etanercept should be reserved for patients in whom other treatments have failed.

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References

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