Review: The addition of infliximab and etanercept to methotrexate is effective in the long term for rheumatoid arthritis

Suarez-Almazor ME, Ortiz Z, Lopez-Olivo M, et al. **Long-term clinical and cost-effectiveness of infliximab and etanercept for rheumatoid arthritis.** Technology Overview no 29. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2007. www.cadth.ca

Clinical impact ratings: Rheumatology ★★★★★★☆

QUESTION

In patients with rheumatoid arthritis (RA), is infliximab (IFX) or etanercept (ETN) effective in the long term?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, BIOSIS Previews, and ToxFile (to September 2005); Cochrane Library (Sept 2005); *Current Contents*; {Health Economic Evaluations Database; clinical trial registries; guideline collections; regulatory sites; Web sites of health technology assessment agencies;}* bibliographies of relevant studies; and drug manufacturers.

Study selection and assessment: Clinical studies that compared ETN or IFX with placebo or other drugs in ≥ 30 patients with RA for ≥ 1 year. Because of the size of the review, this abstract focuses on evidence from randomized controlled trials (RCTs). RCT quality was assessed using the Jadad scale. 8 systematic reviews and 9 RCTs evaluated clinical effectiveness.

Outcomes: Symptom improvement and drug discontinuation.

MAIN RESULTS

The Health Technology Assessment reports and other systematic reviews showed both IFX (3 mg/kg at 0, 2, and 6 wk and every 8 wk thereafter) and ETN (25 mg biweekly) to be effective. In 3 RCTs, IFX plus methotrexate (MTX) was more effective than MTX alone at 54 weeks, particularly in patients who had disease duration > 2 years or in whom methotrexate had failed (Table). ETN was not more effective than MTX but was superior when combined with MTX compared with ETN or MTX alone at 12 months (Table). The addition of IFX or ETN to MTX reduced drug discontinuation relative to MTX alone; ETN alone had fewer drug discontinuations than did MTX alone (Table).

CONCLUSION

In patients with rheumatoid arthritis, the addition of infliximab or etanercept to methotrexate reduced symptoms and drug discontinuation in the long term.

Source of funding: Canadian federal, provincial, and territorial governments.

For correspondence: Dr. M.E. Suarez-Almazor, Baylor College of Medicine, Houston, TX, USA. E-mail mes@bcm.tmc.edu. ■

*Information provided by author.

Infliximab (IFX), 3 mg/kg, or etanercept (ETN), 25 mg, vs methotrexate (MTX) for rheumatoid arthritis*

Outcomes	Comparisons	Group	Number of RCTs	Weighted event rates	Weighted RBI/RRR (95% CI)	NNT (CI)
ACR50 response at 54 wk	IFX + MTX vs MTX	All	3	41% vs 27%	RBI 52% (25 to 85)	8 (5 to 13)
		Disease > 2 y	1	33% vs 7.9%†	RBI 314% (100 to 757)†	4 (3 to 6)
		Disease < 2 y	3	48% vs 31%	RBI 53% (27 to 84)	6 (5 to 10)
		MTX-naïve	2	48% vs 32%	RBI 51% (26 to 82)	7 (5 to 10)
		MTX failure	2	32% vs 7.0%	RBI 326% (111 to 762)	4 (3 to 6)
Stopping drug at 54 wk	IFX + MTX vs MTX	All	3	20% vs 27%	RRR 26% (5 to 42)	15 (8 to 100)
ACR50 response at 12 mo	ETN vs MTX	All	2	48% vs 43%	RBI 13% (–3 to 30)	Not significant
	ETN + MTX vs MTX	All	1	69% vs 43%†	RBI 60% (35 to 90)†	4 (3 to 6)
	ETN + MTX vs ETN	All	1	69% vs 48%†	RBI 43% (22 to 69)†	5 (4 to 9)
Stopping drug at 12 mo	ETN vs MTX	All	2	20% vs 26%	RRR 24% (3 to 41)	17 (9 to 100)
	ETN + MTX vs MTX	All	1	16% vs 30%†	RRR 46% (23 to 62)†	8 (5 to 17)
	ETN + MTX vs ETN	All	1	16% vs 24%†	RRR 31% (–1 to 52)†	Not significant

*ACR50 = American College of Rheumatology improvement response; RCT = randomized controlled trial; other abbreviations defined in Glossary. RBI, NNT, and CI calculated from data in article using a fixed-effects model.
†Not weighted.

COMMENTARY

The review by Suarez-Almazor and colleagues is a summary of 2 other detailed reviews by the same authors and is limited in its scope. Studies and reviews published before September 2005 were included, and only the first-year data were extracted and assessed. As a result, this review may be considered outdated and presents information about therapy initiation only.

The authors point out the relatively modest effects of IFX and ETN alone compared with MTX. This is in part because of the efficacy of MTX when given at optimal doses. 60% of MTX patients in the TEMPO trial had no x-ray progression at 2 years (1). Better results are obtained with combination therapy.

It is not clear how the results of this review translate into clinical practice, where most patients—even in a university environment—would not meet the entry criteria because their disease would not be active enough (2). Moreover, the efficacy seen with MTX requires increasing doses to 15 to 20 mg/wk, which not all rheumatologists do in clinical practice (3).

The most exciting use of tumor necrosis factor-α blockade may be as an induction agent in early RA, as was seen in the BeSt trial (4). With rigorous attention to measuring disease activity scores and titrating therapy based on disease activity levels, 56% of patients were able to come off IFX at a median duration of therapy of 9.9 months. These patients were receiving a median dose of 10 mg/wk of MTX at 2 years.

John Meyerhoff, MD
Johns Hopkins University/Sinai Hospital Program in Internal Medicine
Baltimore, Maryland, USA

References

1. **van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al.** Arthritis Rheum. 2006;54:1063-74.
2. **Sokka T, Pincus T.** Rheum. 2003;48:313-8.
3. **Saraux A, Devauchelle-Pensec V, Engerran L, Flipo RM.** J Rheumatol. 2006;33:1258-65.
4. **van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al.** Arthritis Rheum. 2007;56:2129-2134.