

Review: Anti-tumor necrosis factor antibody therapy for rheumatoid arthritis increases risk for serious infection and malignancy

Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295:2275-85.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Rheumatology ★★★★★☆☆

QUESTION

In patients with rheumatoid arthritis, does treatment with anti-tumor necrosis factor (TNF) antibodies increase the risk for serious infection and malignancy?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Cochrane Library (2005), abstracts from scientific meetings of the European League against Rheumatism and the American College of Rheumatology (1996 to 2005), and drug manufacturers.

Study selection and assessment: Randomized controlled trials (RCTs) that compared anti-TNF antibody therapy (infliximab or adalimumab) with placebo (with or without a traditional disease-modifying antirheumatic drug in each group) in patients with rheumatoid arthritis, with duration of treatment ≥ 12 weeks (range 12 to 54 wk). 9 RCTs ($n = 5014$) met the selection criteria. 2 reviewers independently assessed the RCTs for methodological quality, including randomization, allocation concealment, blinding, intention-to-treat analysis, follow-up,

outcome assessment, and attrition. All RCTs were double-blinded.

Outcomes: Serious infection (requiring antimicrobial therapy or hospitalization) and malignancy.

MAIN RESULTS

Anti-TNF antibody therapy increased risk for both serious infection and malignancy more than placebo (Table). For malignancy, risk was greater in patients receiving a high dose of anti-TNF compared with placebo (odds ratio [OR] 4.3, 95% CI 1.6 to 12) than in those receiving a low dose (OR 1.4, CI 0.3 to 5.7). Direct comparison of high

and low dose also showed increased risk for malignancy with high-dose treatment (OR 3.4, CI 1.4 to 8.2). A dose effect was not observed for serious infection (high dose vs low dose, OR 1.4, CI 1.0 to 2.0).

CONCLUSION

In patients with rheumatoid arthritis, treatment with anti-tumor necrosis factor antibodies increases risk for serious infection and malignancy.

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Adverse effects of anti-tumor necrosis factor (TNF) antibody therapy vs placebo for rheumatoid arthritis at 12 to 54 weeks*

Outcomes	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Anti-TNF	Placebo		
Serious infection	9 (5005)	3.4%	1.7%	98% (30 to 198)	60 (30 to 192)
Malignancy	7 (4620)	0.7%	0.2%	227% (19 to 793)	210 (60 to 2512)

*Abbreviations defined in Glossary; weighted event rates, RRI, NNH, and CI calculated from control event rates and odds ratios in article using a fixed-effects model.

COMMENTARY

Clinical and epidemiologic studies have suggested that immunomodulators, such as TNF inhibitors, may increase the risk for serious infection and malignancy in patients with rheumatoid arthritis (1, 2). However, insufficient numbers of study patients and coexistence of an already altered host immune system have made it difficult to prove such occurrences and to ascribe them to the treatment or the underlying disease.

Bongartz and colleagues have made an admirable effort to address these issues using meta-analysis, but in so doing, they have raised methodological issues that limit the generalizability and applicability of their conclusions. First, although they analyzed > 5000 patients, etanercept was not included in the study; the number of adverse events, especially malignancy, were relatively few; and if one subtracts basal cell cancer and lymphoma from the reported cases, the overall malignancy rate may not be affected. Second, there is some question about the homogeneity of their sample and uncertainty whether a valid meta-analysis of secondary endpoints can be conducted, given that all RCTs had rheumatoid arthritis disease activity as their primary measure. Finally, the risk for malignancy was related to TNF inhibitor dose, but a significant dose effect for infection was not clearly observed, raising the oft-cited concept that malignancy risk is related more to the severity of the rheumatoid arthritis than to the drug used to treat it.

While Bongartz and colleagues have sharpened the debate, they might not have changed the current approach to the treatment of rheumatoid arthritis.

The risk for disease progression still far exceeds the risk for serious adverse effects. Despite the findings of Bongartz and colleagues, it might still be reasonably argued that rheumatologists should continue to prescribe immunomodulatory therapy for their patients with rheumatoid arthritis. However, patients need to be made aware that, although possibly due to the disease rather than to its treatment, the risks for infection and lymphoma are slightly increased.

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References

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