Short-term Risk of Total Malignancy and Nonmelanoma Skin Cancers with Certolizumab and Golimumab in Patients with Rheumatoid Arthritis: Metaanalysis of Randomized Controlled Trials

PIERRE LE BLAY, GAEL MOUTERDE, THOMAS BARNETCHE, JACQUES MOREL, and BERNARD COMBE

ABSTRACT. ***Objective.*** To assess the risk of total malignancy and nonmelanoma skin cancers (NMSC) in patients with rheumatoid arthritis (RA) receiving certolizumab and golimumab through a metaanalysis of data from randomized control trials (RCT).

Methods. We systematically reviewed the literature up to May 2011 in Medline databases, as well as abstracts from the 2009 and 2010 annual meetings of the European League Against Rheumatism and the American College of Rheumatology. Mantel-Haenszel method was used to determine a common odds ratio (OR). Statistical heterogeneity was assessed by chi-square Q test. We selected only RCT including more than 30 RA subjects randomly assigned to an anti-tumor necrosis factor (TNF) or a nonbiological disease-modifying antirheumatic drug (DMARD) control group.

Results. The literature search identified 793 articles; 6 (2 with certolizumab and 4 with golimumab) were selected for metaanalysis. A total of 2710 patients received at least 1 dose of certolizumab or golimumab. For anti-TNF-treated patients, 18 cancers (excluding NMSC) and 9 NMSC were observed versus 4 cases of total malignancy and 3 NMSC in control groups. Metaanalysis revealed a pooled OR of 1.06 (95% CI 0.39–2.85) for risk of total malignancy and 0.69 (95% CI 0.23–2.11) for risk of NMSC with certolizumab and golimumab versus DMARD. Heterogeneity was not significant.

Conclusion. Metaanalysis of RCT of golimumab and certolizumab did not find an increased risk of total malignancy and NMSC. These results must be confirmed with longterm extension studies and registry studies, and careful monitoring remains mandatory. (First Release March 1 2012; J Rheumatol 2012;39:712–15; doi:10.3899/jrheum.110982)

Key Indexing Terms:

CERTOLIZUMAB GOLIMUMAB MALIGNANCY
NONMELANOMA SKIN CANCER RHEUMATOID ARTHRITIS METAANALYSIS

For more than 10 years, tumor necrosis factor (TNF) antagonists have shown effectiveness for rheumatoid arthritis (RA) and they are now widely used for treating active RA. In addition to adalimumab, etanercept, and infliximab, 2 new anti-TNF monoclonal antibodies, certolizumab and golimumab, have been approved for RA[1,2,3,4,5,6,7,8].

In 2006, a metaanalysis of randomized controlled trials (RCT) of adalimumab and infliximab suggested that these anti-TNF monoclonal antibodies might be associated with an increased risk of malignancy[9]. However, data including RCT with etanercept did not find a significantly increased risk in patients with RA[10]. Nevertheless, doubt remains concerning the specific risk for nonmelanoma skin cancers (NMSC) in longterm extension studies[11] and in a recent metaanalysis using patient-level data[12].

Our objective was to assess the risk of total malignancy and NMSC in patients with RA receiving certolizumab or golimumab; we performed a systematic review and metaanalysis based on data from RCT of those 2 newly licensed anti-TNF products whose results have not been included in previous metaanalyses.

MATERIALS AND METHODS

Study selection. We performed a systematic review of the literature up to May 2011. Bibliographic references were selected from Medline databases and abstracts from 2009 and 2010 annual meetings of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR).

We searched Medline with PubMed using the following key terms: arthritis, rheumatoid [MeSH] OR rheumatoid arthritis [all fields] AND (neoplasm [MeSH] OR safety [MeSH]) OR (neoplasm or safety) [all fields] AND (biological therapy [MeSH] OR tumor necrosis factor-alpha [MeSH]

From the Rheumatology Department, Lapeyronie Hospital, Montpellier 1 University, UMR 5535, Montpellier; and the Rheumatology Department, Bordeaux University Hospital, Bordeaux, France.

P. Le Blay, MD; G. Mouterde, MD, Rheumatology Department, Lapeyronie Hospital, Montpellier 1 University; T. Barnetche, MD, Rheumatology Department, Bordeaux University Hospital; J. Morel, PhD; B. Combe, PhD, Professor, Rheumatology Department, Lapeyronie Hospital, Montpellier 1 University.

Address correspondence to Prof. B. Combe, Rheumatology Department, Lapeyronie Hospital, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France. E-mail: b-combe@chu-montpellier.fr

Accepted for publication November 9, 2011.

OR antibodies, monoclonal [MeSH]) OR (monoclonal antibody OR biological response modifier OR tumor necrosis factor-alpha OR tumor necrosis factor alpha antibody OR tumor necrosis factor-alpha OR anti tumor necrosis factor) [all fields] OR certolizumab pegol [all fields] OR golimumab [all fields] OR (Drug Combination Disease (W) Modifying (W) Anti (W) Inflammatory (W) Drug OR Dmard) [all fields]. In addition, reference lists of the reports initially identified were manually searched to identify additional relevant reports.

To be included, RCT of golimumab and certolizumab had to include more than 30 RA subjects in intention-to-treat studies, randomly assigned to an anti-TNF or a nonbiological DMARD control group for at least 10 weeks. Studies with a placebo control group and treatment arms of combination biological therapies were excluded.

Total malignancy was considered as all solid (including melanoma and excluding NMSC) and hematological cancers. NMSC included basal and squamous cell skin cancers.

Statistical analysis. The pooled odds ratio (OR) for patients receiving certolizumab or golimumab versus synthetic disease-modifying antirheumatic drug (DMARD) therapy was determined using Mantel-Haenszel methods, with a continuity correction designed for sparse data (adding 0.5 to each arm of such studies). Moreover, additional sensitivity analyses were conducted, describing the stability of the results when either 1 or 2 "virtual" events were used in case no cancer event had been observed in the trials.

Analyses involved use of Revman 5.0 software developed by the Nordic Cochrane Center. OR and 95% CI are shown on forest plots. Statistical heterogeneity was assessed by the chi-square Q test, with a significance level of 0.05.

RESULTS

The literature search identified 793 articles, from which 72 were preselected on the basis of the title and abstract. After reading full texts, we selected 6 RCT with a synthetic DMARD comparison group, 2 with certolizumab[6,8], and 4 with golimumab[1,2,3,4] (Figure 1). A total of 2710 patients received at least 1 dose of certolizumab or golimumab, compared with 783 who received synthetic DMARD. For patients treated with anti-TNF inhibitors, 18 cancers were observed (excluding NMSC): 2 each breast, tongue, colon, and lung cancers; 1 each uterus, esophageal, liver, adrenal, papilloma, testicle, bladder, and ovarian cancers; and 2 hematological neoplasms. Only 4 cases of malignancy were observed in control groups. A metaanalysis of data from these 6 studies with patients receiving synthetic DMARD as control group revealed a pooled OR for risk of total malignancy with certolizumab and golimumab of 1.06 (95% CI 0.39–2.85) versus DMARD, without significant heterogeneity (Figure 2).

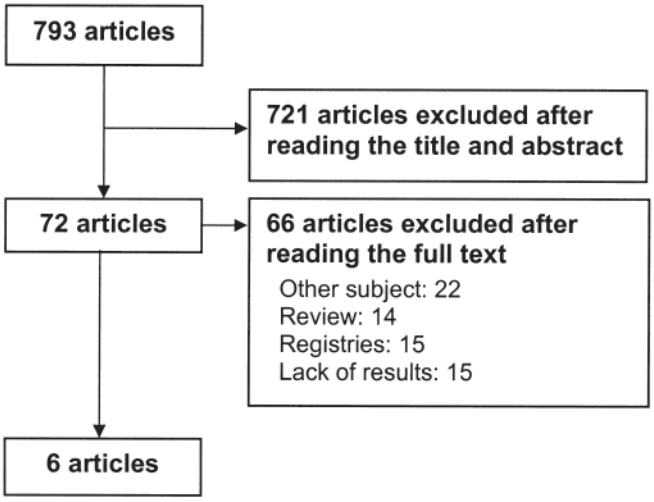

Figure 1. The selection process of articles.

Nine cases of NMSC were observed in anti-TNF groups, compared with 3 in DMARD groups, and the pooled OR was 0.69 (95% CI 0.23–2.11; Figure 3).

Sensitivity analyses did not significantly modify our results, as the same trend toward no significantly increased risk was observed (data not shown).

DISCUSSION

A relation between RA and carcinogenesis was suggested for many years because some registry studies found an increased risk of certain cancers (lung, lymphoma, NMSC) in patients with RA as compared with the general population, regardless of the treatment[13,14].

Recently, Leombruno, *et al*[10], in a metaanalysis, analyzed 17 RCT of adalimumab, etanercept, and infliximab compared to DMARD in RA. The OR was 1.34 (95% CI 0.75–2.39) for total malignancy. Askling, *et al*[12], in another metaanalysis of RCT of these 3 TNF antagonists in RA (31 RCT) and other diseases (43 RCT), used a strict method listing different types of malignancy, with predefined terms that were as specific as possible irrespective of report in the trial, in order to reduce missing information. They did not find an increased risk of total malignancy, but the risk of NMSC was significantly higher with TNF antagonists (HR 2.02, 95% CI 1.11–3.95)[12].

In order to complete the metaanalysis of these 3 widely used TNF antagonists, and because few RCT of these biologics had been recently published, we aimed to assess the risk of malignancy especially with 2 new monoclonal antibodies by performing a metaanalysis of data from RCT of these 2 drugs. We chose to pool total malignancy (without NMSC) as 1 group and NMSC-only as the other, because of observations of a possible increased risk of NMSC with TNF antagonist treatment[11,12] and differences in prognosis of these cancers. This distinction had been made in previous metaanalyses[10,12]. We excluded placebo-control trials in order to compare the risk of malignancy with these 2 new TNF antagonists with the "gold standard" in RA. Data extracted from RCT enable a strict comparison with referent treatment and a comprehensive inventory of safety. However, because of their short followup (only 2 studies had data at 52 weeks and one at 48 weeks; the others were 24-week followup studies) and small sizes of different groups, RCT are limited in assessing uncommon adverse effects such as cancer. This is a significant bias for safety analysis we found in all metaanalyses of RCT.

This first metaanalysis of risk of malignancy with use of

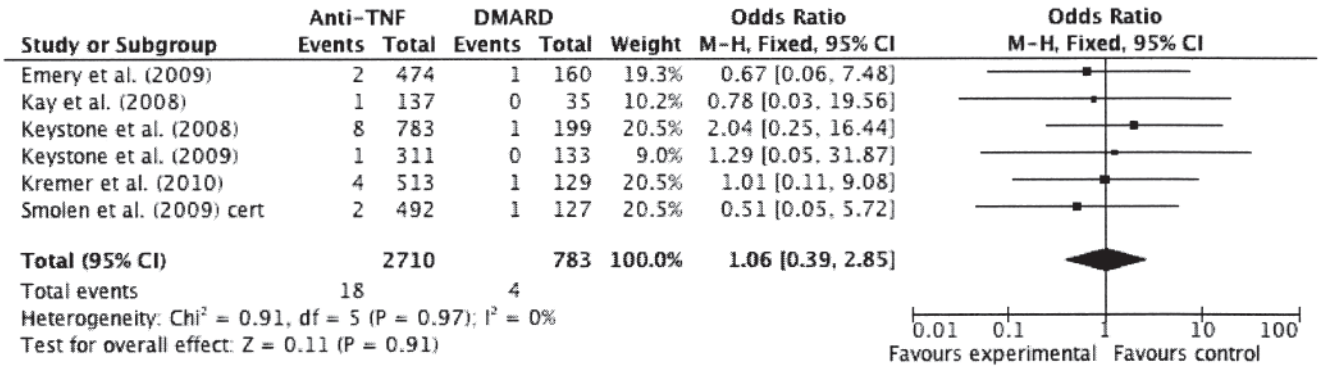

Figure 2. Risk estimates of total malignancy (excluding nonmelanoma skin cancers) reported in randomized controlled trials of patients with rheumatoid arthritis treated with golimumab and certolizumab. TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drug; M-H: Mantel-Haenszel test.

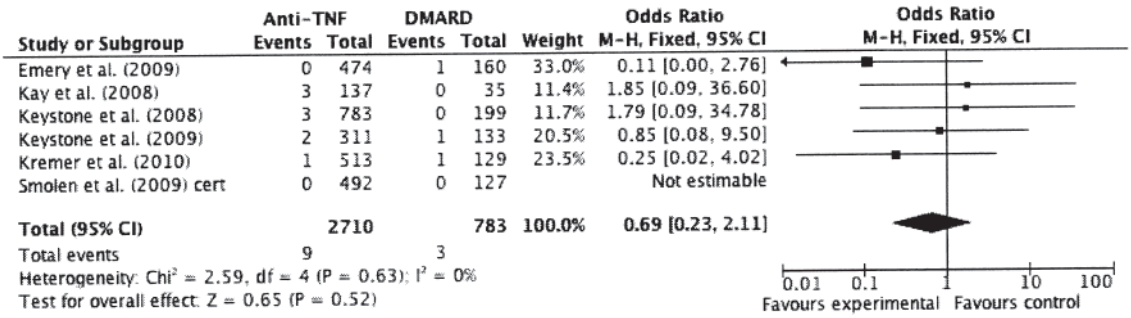

Figure 3. Risk estimates of nonmelanoma skin cancers reported in randomized controlled trials of patients with rheumatoid arthritis treated with golimumab and certolizumab. TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drug; M-H: Mantel-Haenszel test.

certolizumab and golimumab is reassuring, as we found no increased risk of total malignancy and NMSC. However, these results must be confirmed with longterm extension studies and registry studies, and careful monitoring remains mandatory.

REFERENCES

1. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60:2272-83.
2. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: A randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58:964-75.
3. Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum 2010;62:917-28.
4. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor (alpha) given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: The GO-FORWARD Study. Ann Rheum Dis 2009;68:789-96.
5. Smolen J, Kay J, Doyle M, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): A multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374:210-21.
6. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: The RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68:797-804.
7. Fleischmann R, Vencovsky J, Van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: The FAST4WARD study. Ann Rheum Dis 2009;68:805-11.
8. Keystone E, Heijde D, Mason D, Landewe R, van Vollenhoven R, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58:3319-29.
9. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. 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.
10. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: Meta

and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68:1136-45.
11. Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis 2009;68:1863-9.
12. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: Meta-analysis of randomized controlled trials of adalimumab, etanercept and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011;20:119-30.
13. Geborek P, Bladström A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005;64:699-703.
14. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1421-6.