BRIEF OBSERVATION

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All-cause Mortality Associated with TNF-α Inhibitors in Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

OBJECTIVE: To compare mortality data obtained from randomized controlled trials for the 5 tumor necrosis factor-α (TNF-α) inhibitors used in the treatment of rheumatoid arthritis.

METHODS: A systematic review of articles published up to November 2014 was performed using electronic databases. We included randomized, controlled trials, with a follow-up period of at least 24 weeks, comparing TNF-α inhibitors to placebo or disease-modifying antirheumatic drugs. The primary outcome was the occurrence of all-cause mortality.

RESULTS: Twenty-three studies were selected. These articles included 6525 patients in the anti-TNF-α group and 3523 in the control group. The duration of patient follow-up ranged from 24 to 104 weeks. The risk of all-cause mortality in patients receiving TNF-α inhibitors was not significantly different from those receiving the comparator (odds ratio 1.32; 95% confidence interval, 0.76-2.29). Subgroup analyses with respect to the molecule used, the dose received, the use of TNF-α inhibitors as monotherapy or combination therapy, or the quality of the trial did not modify the findings.

CONCLUSION: This meta-analysis performed on a large number of patients and including the 5 TNF-α inhibitors currently available shows no increased risk of medium-term all-cause mortality in patients with rheumatoid arthritis.

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KEYWORDS: Meta-analysis; Mortality; Rheumatoid arthritis; TNF-α inhibitors

Tumor necrosis factor-α (TNF-α) inhibitors are the most widely used first-line biologic therapy for the treatment of rheumatoid arthritis. Much has been written on the concern that TNF-α inhibitors may increase the risk of malignancy, infections, and other serious adverse events.[1,2] However, studies of the potential risks of this drug class on the "hard endpoint" mortality are scarce and have provided conflicting results.[3] A previous meta-analysis reported no evidence of increased mortality associated with any TNF-α inhibitor in rheumatoid arthritis. However, the analysis was limited to the 3 TNF-α inhibitors available at this period and mainly included short-term safety data.[4] Thus, our aim was to assess the risk of medium-term all-cause mortality upon the 5 currently available TNF-α inhibitors in rheumatoid arthritis through a meta-analysis of randomized controlled trials.

METHODS

Data Sources and Literature Search

We searched randomized controlled trials using MEDLINE via PubMed, the Cochrane databases, Embase, Google Scholar, and manual searches of reference lists from systematic reviews and original publications. Studies published in English were identified from January 1, 2000 to November 1, 2014. The search terms included *TNF alpha inhibitors; adalimumab; etanercept; certolizumab pegol; infliximab; golimumab; rheumatoid arthritis; Randomized controlled trials, mortality; English; All adults*. Our

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research was limited to English language and human clinical trials.

Inclusion Criteria

We defined the target population as adults with rheumatoid arthritis diagnosed according to the 1987 American College of Rheumatology criteria.[5] Interventions included all 5 currently available TNF-α inhibitors. Eligible comparators included placebo and conventional disease-modifying antirheumatic drugs (DMARDs). The primary outcome of this study was the occurrence of all-cause mortality defined on an intention-to-treat basis. To better reflect the drug effect on the potential risk of death, included studies have to report a minimum of 24 weeks of the study duration.

CLINICAL SIGNIFICANCE

- Tumor necrosis factor-α inhibitors show no increased risk of medium-term all-cause mortality.
- The type of molecule and the dose received do not modify this finding.

Methodological Quality

The articles that fulfilled the inclusion criteria underwent quality appraisal by using the Jadad scale.[6]

Data Extraction

Two investigators (LP and JA) independently extracted data from articles using a customized form, available from the authors. Disagreements were resolved by consensus.

Statistical Analysis

We used the Mantel-Haenszel method for calculating the weighted summary odds ratio under the fixed-effect model. Next, the heterogeneity was incorporated to calculate summary odds ratios under the random-effects model (DerSimonian and Laird).[7] Statistical heterogeneity was tested by Q-test (χ^2) and I^2 statistic calculation.[8] All statistical tests and creation of forest plots were conducted with MedCalc software (v11.4.4; Ostend, Belgium). Additional subgroup analyses were planned to check whether they would substantially change the findings.

RESULTS

Included Studies

The results of the article selection process are reported in Figure 1. Among the 495 studies initially analyzed, 23 studies fulfilled our inclusion criteria (Table 1).[9-31] The median study duration was 46 weeks (range: 24 to 104 weeks). This analysis included 10,048 patients: 6525 were treated with TNF-α

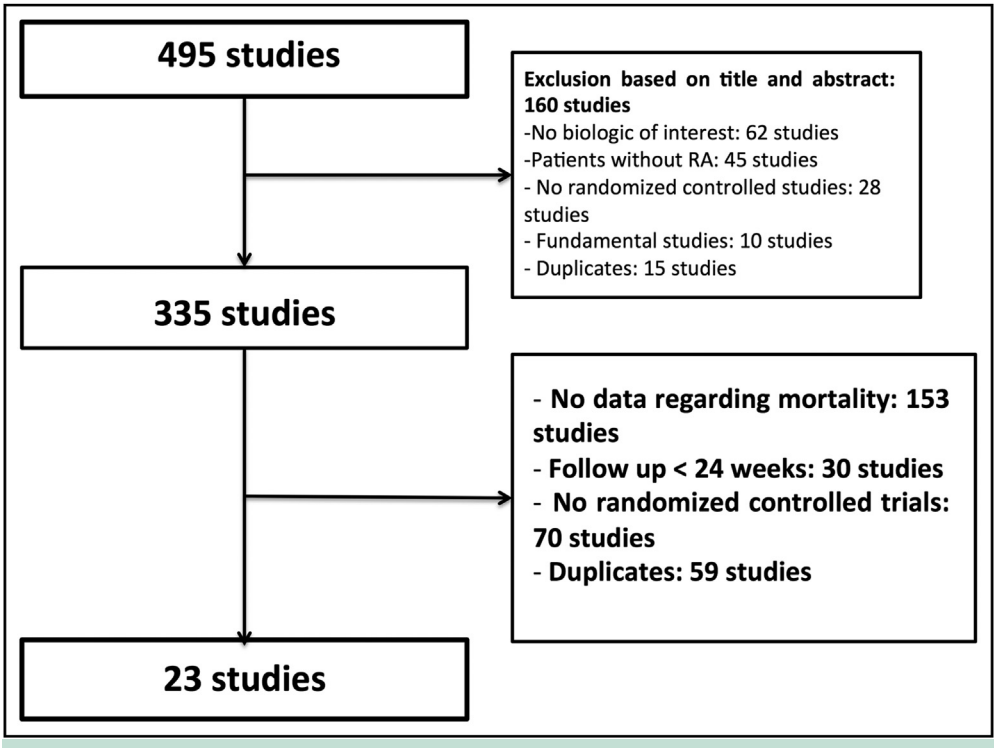

Figure 1 Flow diagram of articles evaluated for inclusion and exclusion. RA = rheumatoid arthritis.

Table 1 Characteristics of Trials Included in the Analysis

Reference	Mean Disease Duration (Y)	Placebo		TNF-α Inhibitor			Trial Duration (Wk)	Jadad Score
		n	Type	Type	Dose	n		
Kremer et al, 2010[9]	8.3	129	Methotrexate	Golimumab	2-4 mg/kg/3 mo	257	48	4
Emery et al, 2009[10]	3.4	160	Methotrexate	Golimumab	50 or 100 mg/4 wk	318	24	5
Quinn et al, 2005[11]	0.6	10	Methotrexate	Infliximab	3 mg/kg	10	54	4
St. Clair et al, 2004[12]	0.9	291	Methotrexate	Infliximab	3 or 6 mg/kg	749	54	5
Keystone et al, 2004[13]	11.0	200	Methotrexate	Adalimumab	20 mg/wk or 40 mg/2 wk	419	52	3
Furst et al, 2003[14]	10.4	318	Disease-modifying antirheumatic drugs	Adalimumab	40 mg/2 wk	318	24	3
Smolen et al, 2013[15]	6.8	200	Methotrexate	Etanercept	25 or 50 mg/wk	404	28	5
Klareskog et al, 2004[16]	6.8	228	Methotrexate	Etanercept	25 mg/2 wk	231	52	4
Combe et al, 2006[17]	6.2	50	Sulfasalazine	Etanercept	25 mg/2 wk	101	24	3
Smolen et al, 2009[18]	6.2	127	Methotrexate	Certolizumab	200 mg or 400 mg/2 wk	492	24	3
Fleischmann et al, 2009[19]	9.6	109	Placebo	Certolizumab	400 mg/2 wk	111	24	5
Keystone et al, 2008[20]	6.2	199	Methotrexate	Certolizumab	200 or 400 mg/2 wk	783	52	4
Durez et al, 2007[21]	0.4	14	Methotrexate	Infliximab	3 mg/kg	15	46	2
Lipsky et al, 2000[22]	10.6	88	Methotrexate	Infliximab	3-10 mg/kg	340	52	3
Kavanaugh et al, 2013[23]	0.3	517	Methotrexate	Adalimumab	40 mg/2 wk	515	78	4
Van Vollenhoven et al, 2011[24]	8.6	76	Methotrexate	Adalimumab	40 mg/2 wk	79	26	2
Choy et al, 2012[25]	9.6	121	Methotrexate	Certolizumab	400 mg/2 wk	126	24	5
Breedveld et al, 2006[26]	0.8	257	Methotrexate	Adalimumab	40 mg/2 wk	268	52	3
Miyasaka et al, 2008[27]	9.4	87	Placebo	Adalimumab	20-40 mg or 80 mg/2 wk	265	24	3
van de Putte et al, 2004[28]	10.9	110	Placebo	Adalimumab	20-40 mg/wk or 2 wk	434	26	5
Schiff et al, 2008[29]	7.7	110	Methotrexate	Infliximab	3 mg/kg	165	24	4
Leirisalo-Repo et al, 2013[30]	0.3	49	Disease-modifying antirheumatic drugs	Infliximab	3 mg/kg	50	104	5
Bejarano et al, 2008[31]	0.7	73	Methotrexate	Adalimumab	Not reported	75	56	5

TNF = tumor necrosis factor.

Table 2 Events Reported in Trials

			Deaths, n		Cause of Death		
Reference	TNF-α Inhibitor	Dose of TNF-α Inhibitor	Placebo	TNF-α Inhibitor	Placebo	TNF-α Inhibitor	Dose
Kremer et al, 2010[9]	Golimumab	2-4 mg/kg/3 mos	0	1	0	Myocardial infarction	Normal/high
Emery et al, 2009[10]	Golimumab	50 or 100 mg/4 wk	0	2	0	Suicide, cardiorespiratory arrest after surgery	Normal/high
Quinn et al, 2005[11]	Infliximab	3 mg/kg	0	0	0	0	Normal
St Clair et al, 2004[12]	Infliximab	3 or 6 mg/kg	2	2	Respiratory failure due to methotrexate, upper gastrointestinal bleed	Cardiac arrest, metastatic pancreatic cancer	Normal/high
Keystone et al, 2004[13]	Adalimumab	20 mg/wk or 40 mg/2 wk	0	3	0	Multiple fractures, urosepsis, complications of chemotherapy for lymphoma	Normal
Furst et al, 2003[14]	Adalimumab	40 mg/2 wk	0	1	0	Necrotizing fasciitis	Normal
Smolen et al, 2013[15]	Etanercept	25 or 50 mg/wk	0	2	0	Pulmonary embolism, septicemia	Low/normal
Klareskog et al, 2004[16]	Etanercept	25 mg 2/wk	1	1	Pulmonary embolism	Stroke and pneumonia	Normal
Combe et al, 2006[17]	Etanercept	25 mg 2/wk	0	0	0	0	Normal
Smolen et al, 2009[18]	Certolizumab	200 mg or 400 mg/2 wk	0	2	0	Myocardial infarction, fracture and shock	Low/normal
Fleischmann et al, 2009[19]	Certolizumab	400 mg/2 wk	0	0	0	0	Normal
Keystone et al, 2008[20]	Certolizumab	200 or 400 mg/2 wk	1	5	Myocardial infarction	Hepatic neoplasm, cardiac arrest, cerebral stroke, myocardial necrosis, cardiac arrest	Low/normal
Durez et al, 2007[21]	Infliximab	3 mg/kg	0	0	0	0	Normal
Lipsky et al, 2000[22]	Infliximab	3-10 mg/kg	3	5	Not reported	Not reported	Normal/high
Kavanaugh et al, 2013[23]	Adalimumab	40 mg/2 wk	1	6	Sudden death	Septic shock, right ventricular failure, unknown cause, acute respiratory distress, two interstitial lung disease	Normal
Van Vollenhoven et al, 2011[24]	Adalimumab	40 mg/2 wk	0	0	0	0	Normal
Choy et al, 2012[25]	Certolizumab	400 mg/2 wk	0	0	0	0	Normal
Breedveld et al, 2006[26]	Adalimumab	40 mg/2 wk	1	1	Pneumonia	Ovarian cancer	Normal
Miyasaka et al, 2008[27]	Adalimumab	20-40 mg or 80 mg/2 wk	0	2	0	Interstitial lung disease, cerebral hemorrhage	Low/normal/high
van de Putte et al, 2004[28]	Adalimumab	20-40 mg/wk or 2 wk	1	3	Complications of bowel obstruction	Metastatic adenocarcinoma, cholangiocarcinoma, myocardial infarction	Low/normal/high
Schiff et al, 2008[29]	Infliximab	3 mg/kg	0	1	0	Fibrosarcoma	Normal
Leirisalo-Repo et al, 2013[30]	Infliximab	3 mg/kg	0	1	0	Not reported	Normal
Bejarano et al, 2008[31]	Adalimumab	Not reported	0	0	0	0	Not reported

TNF = tumor necrosis factor.

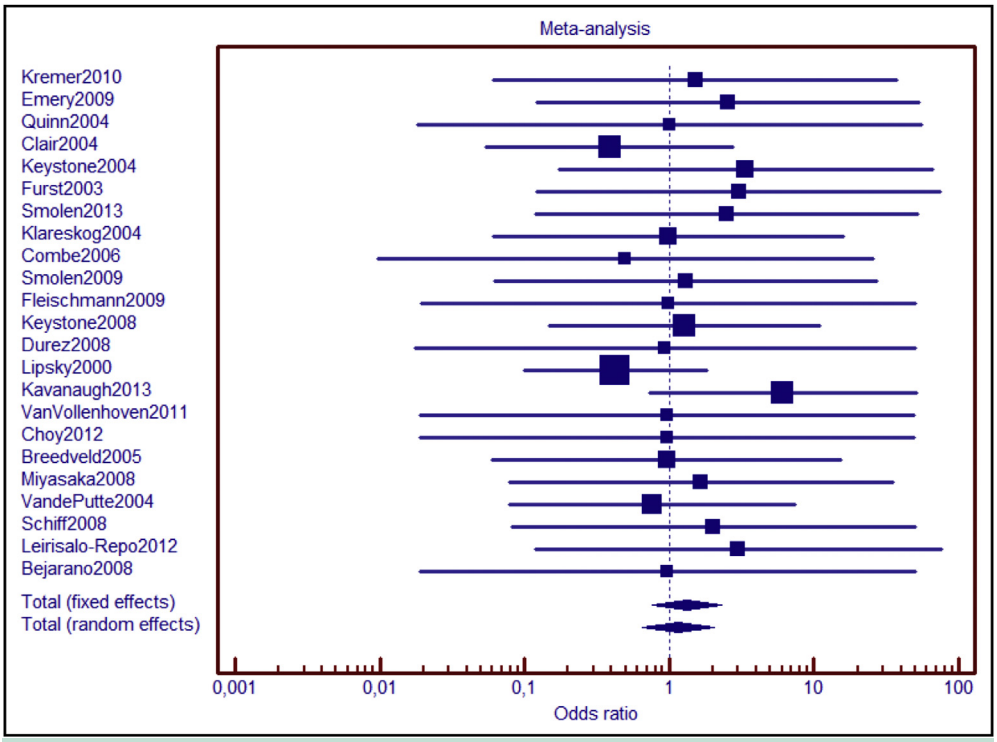

Figure 2 Forest plot of trials comparing tumor necrosis factor-α inhibitors to comparators for the risk of all-cause mortality in patients with rheumatoid arthritis. Heterogeneity: Q = 7.87; *df* = 22, *P* = .99, $I^2 < 25\%$.

inhibitors and 3523 were treated with placebo or conventional DMARDs.

Primary Outcome: Mortality of Any Cause Upon TNF-α Inhibitors Compared with Controls

During the study duration, 34/6525 (0.52%) deaths were observed in patients treated with TNF-α inhibitors, compared with 10/3523 (0.28%) deaths in those treated with conventional DMARDs/placebo (*P* = .113) (**Table 2**).[9-31] Thus, the risk of death of any cause in patients receiving TNF-α inhibitors was not significantly different from those receiving the comparator (odds ratio [OR] 1.32; 95% confidence interval [CI], 0.76-2.29) (**Figure 2**). The results were consistent across trials (Q = 7.87, *P* = .99, and $I^2 < 25\%$).

Subgroup analysis within the type of comparator did not modify previously observed results. The OR of mortality of patients receiving TNF-α inhibitors used as monotherapy vs placebo was 1.04 (95% CI, 0.20-5.34), and the OR of mortality of patients receiving TNF-α inhibitors used in combination therapy vs conventional DMARDs was 1.36 (95% CI, 0.76-2.43).

Secondary Analyses

Subgroup Analyses with Respect to Each Molecule. Individually, each molecule analyzed separately did not show an increased risk of mortality of any cause (**Table 3**).

Subgroup Analysis with Respect to the Dose of TNF-α Inhibitors. To address the potential dose impact, we compared the mortality event rates according to TNF-α inhibitor dose (high dose, defined by a dose higher than usual TNF-α inhibitor dose as per package insert, vs usual dose). High dose of TNF-α inhibitors was not significantly associated with a significant increase in risk of mortality (OR 0.97; 95% CI, 0.26-3.54 vs 1.43; 95% CI, 0.79-2.59 for the usual dose).

Table 3 Odds Ratio for All-cause Mortality According to the Molecule Used

	Total	Adalimumab n = 2373	Golimumab n = 575	Certolizumab n = 1512	Infliximab n = 1329	Etanercept n = 736
Rheumatoid arthritis (OR, 95% CI)	1.32 95% CI, 0.76-2.29	2.17 95% CI, 0.83-5.68	2.02 95% CI, 0.23-18.19	1.19 95% CI, 0.27-5.18	0.70 95% CI, 0.27-1.81	1.28 95% CI, 0.23-7.25

CI = confidence interval; OR = odds ratio.

Subgroup Analysis with Respect to the Quality of Evidence. Most of our comparison analyses reached a high level of quality of evidence, with a mean Jadad score of 3.87 ± 1.01 (Table 1).[9-31] We compared studies with a high quality (Jadad score >3) to those with a lower quality (Jadad score ≤ 3). The results did not appear to differ substantially. In high-quality studies, the OR for mortality of any cause was 1.60 (95% CI, 0.78-3.30), and in lower-quality studies, the OR was 0.99 (95% CI, 0.42-2.31).

To help address the potential impact of the calendar time, we also compared mortality according to calendar year of publication (before and after 2006). The summary ORs for mortality were both not significant for these 2 time periods (0.80; 95% CI, 0.37-1.76 before and 2.03; 95% CI, 0.91-4.52 after 2006).

DISCUSSION

A recent meta-analysis has underlined the higher risk of overall serious adverse events in certolizumab pegol-treated patients and the significant increase in the risk of serious infections in patients on adalimumab, certolizumab pegol, and infliximab, which might suggest a potential higher risk of mortality.[1] This hypothesis has not been confirmed in our meta-analysis, which covered the same time period and compared the 5 currently available TNF-α inhibitors for the risk of mortality, an undisputed hard endpoint. Indeed, the use of TNF-α inhibitors is not associated in our study with an increased risk of medium-term mortality.

Several registries have suggested a reduction of the risk of mortality in patients with rheumatoid arthritis treated with TNF-α inhibitors.[32-34] Several factors may explain this discrepancy, especially the inclusion of highly selected patients in randomized controlled trials compared with unselected patients in registries, and the longer time of drug exposure in the latter. This may suggest that registries may be more adequate to address the impact of TNF-α inhibitors on overall mortality. However, our results are consistent with data extracted from the British Society for Rheumatology Biologics Registers and with the meta-analysis of Leombruno.[4,35]

Strengths of our meta-analysis are its large sample size, an indirect comparison among the 5 available molecules, the presence of a control group obtained through a process of randomization, the quality of data extracted from a majority of high-quality randomized controlled trials, and the absence of heterogeneity among included trials. Limitations of our meta-analysis included the generalization of our results and the absence of long-term exposition on TNF-α inhibitors. Insufficient data were provided to perform a subgroup analysis according to the duration of use of TNF-α inhibitors. Moreover, effect of TNF-α inhibitors on mortality may occur after discontinuation of these drugs, and this aspect could not be assessed in our meta-analysis.

In conclusion, this meta-analysis shows that treatment with TNF-α inhibitors is not associated with a higher risk of medium-term mortality of any cause in patients with rheumatoid arthritis. These results are reassuring for this duration, given that these therapies are highly effective at controlling symptoms and reducing disability and damage. Further studies are warranted to assess the long-term effect of TNF-α inhibitors on mortality.

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APPENDIX

Supplementary references accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.07.020.

Appendix 1: References of included studies

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