

Golimumab for Rheumatoid Arthritis: A Systematic Review

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ABSTRACT. Objective. To perform a Cochrane systematic review of benefit (American College of Rheumatology 50% improvement criteria; ACR50) and safety (adverse events and withdrawals) of golimumab in patients with rheumatoid arthritis (RA).

Methods. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), OVID Medline, CINAHL, Embase, Science Citation Index (Web of Science), and Current Controlled Trials databases for randomized or controlled clinical trials of golimumab compared to placebo or disease-modifying antirheumatic drug in adults with RA. Two authors independently selected appropriate studies and abstracted study characteristics and safety and efficacy data and performed risk-of-bias assessment. We calculated mean differences for continuous measures, and relative risks for categorical measures.

Results. Four randomized controlled trials with 1231 golimumab-treated and 483 placebo-treated patients were included. Of these, 436 were treated with golimumab at 50 mg every 4 weeks [a dosage approved by the US Food and Drug Administration (FDA)]. At an average of 4–6 months, compared to patients treated with placebo and methotrexate (MTX), patients treated with the FDA-approved dosage of golimumab and MTX were 2.6 times more likely to reach ACR50 ($p = 0.005$, 95% CI 1.3, 4.9; absolute percentage, 38% vs 15%) and 0.5 times as likely to have overall withdrawals ($p = 0.005$, 95% CI 0.3, 0.8; absolute percentage, 5% vs 10%). Golimumab-treated patients were significantly more likely than those taking placebo to achieve remission (22% vs 4%; $p < 0.00001$), and to have improvement in functional ability on the Health Assessment questionnaire [0.2 points lower ($p < 0.00001$, 95% CI 0.25, 0.15); absolute risk difference, -20% (95% CI -25% to -15%); relative percentage difference, -11% (95% CI -14% to -8.3%)]. The studies were too small and short to be powered sufficiently for safety outcomes, but no substantive statistically significant differences were noted between golimumab and placebo regarding adverse events, serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events, and withdrawals due to inefficacy and deaths.

Conclusion. At the approved dosage, in patients with active RA taking background MTX, golimumab is significantly more beneficial than placebo. The short-term safety profile is reasonable. Longterm surveillance studies are needed for safety assessment. (J Rheumatol First Release May 1 2010; doi:10.3899/jrheum.091466)

Key Indexing Terms:

GOLIMUMAB RHEUMATOID ARTHRITIS EFFICACY SAFETY SYSTEMATIC REVIEW

Rheumatoid arthritis (RA) is a systemic disease characterized by destructive, inflammatory polyarthritis affecting small and large joints¹. RA has a significant effect on both

patient-reported quality of life and function (HRQOL)^{2,3} and can sometimes lead to serious work disability^{4,5}. Inflammation in RA is characterized by the activation of

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Dr. J.A. Singh has received speaker honoraria from Abbott, research and travel grants from Takeda, Savient, Wyeth and Amgen, and consultant fees from Savient and URL Pharmaceuticals. Dr. G. Singh has received honoraria/consultant/research grants from Centocor, Abbott, Amgen, and Johnson & Johnson.

This is a version of a Cochrane Review, which will be available in The Cochrane Library, Issue 1, 2010.

The views expressed in this article are those of the authors and do not

necessarily reflect the position or policy of the Department of Veterans Affairs.

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Accepted for publication February 3, 2010.

many immune cells, including but not limited to T cells, B cells, and macrophages⁶. Such immune cells secrete various cytokines⁷, i.e., tumor necrosis factor- α (TNF- α) and interleukins^{7,8}, which in turn lead to inflammation, and joint and bone destruction. Lately, much of the focus of treatment of RA has been on inhibition of TNF- α , since it is thought to play a central role in joint inflammation⁹.

The pharmacological therapeutic strategies for RA include nonsteroidal antiinflammatory drugs (NSAID), traditional disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX), and newer biologic DMARD. The biologic DMARD include TNF- α inhibitors and non-TNF biologic DMARD¹⁰. TNF- α inhibitors include etanercept¹¹, infliximab¹², and adalimumab¹³; recently, golimumab has been approved for RA in several countries (USA, Canada, European Union, Japan, and others). Non-TNF biologic DMARD (and respective targets) include anakinra (interleukin 1)¹⁴, abatacept (costimulatory molecule, CD28)¹⁵, and rituximab (B cells)¹⁶.

Golimumab is a humanized inhibitor of TNF- α ¹⁷. It neutralizes TNF- α by binding to it, thus interfering with its binding to the TNF- α receptors on cell surfaces. TNF- α plays a key role in the inflammation and joint destruction that are the hallmarks of RA⁹. The approved dosage for treatment of RA with golimumab is 50 mg subcutaneous injection given once a month¹⁸. This frequency of administration is lower than all the other biologics except for abatacept (monthly subcutaneous), infliximab [intravenous (IV) every 8 weeks], and rituximab (3 doses over 6 weeks intravenously, then no infusions for 6 months). It is important to know whether, with this low frequency, the biologic therapy results in improvement that is judged important by patients and their clinicians.

MATERIALS AND METHODS

Criteria for considering studies for this review. All studies had to be randomized controlled trials (RCT) or controlled clinical trials (methods of allocating participants to a treatment that are not strictly random, e.g., date of birth, hospital record number, or alternation). There was no language restriction on included studies. An expert librarian searched the following databases for randomized or quasirandomized trials of golimumab in RA: (1) The Cochrane Central Register of Controlled Trials (CENTRAL), through The Cochrane Library, Wiley InterScience (www.thecochranelibrary.com), issue 2, 2009; (2) OVID Medline, 1966-2009; (3) CINAHL (through EBSCOHost), 1982-2009; (4) Embase 1980-2009; (5) Science Citation Index (Web of Science) 1945-2009; and (6) Current Controlled Trials.

We included studies involving adults age 18 years or older, with RA, meeting the 1987 American College of Rheumatology (ACR) classification criteria for RA¹⁹ (Table 1). Interventions compared were golimumab alone or in combination with DMARD or biologics versus placebo plus MTX or golimumab alone or in combination with DMARD or biologics compared to other DMARD or biologics. There were no restrictions with regard to dosage or duration of intervention. We assessed safety and efficacy at all dosages including the approved dosage of 50 mg every 4 weeks.

Major outcomes. Outcomes were chosen based on recommendations regarding 7 key outcomes for the summary of findings table by the Cochrane Musculoskeletal Group. Major outcomes included the ACR 50%

improvement criteria (ACR50), Disease Activity Score (DAS) remission (DAS < 1.6 or DAS 28-joint count < 2.6), function measured by Health Assessment Questionnaire (HAQ) score or modified HAQ calculated as score changes^{20,21}, the proportion achieving minimally clinically important difference on HAQ ≥ 0.22 ²², number of adverse events, number of serious adverse events (SAE), number of withdrawals due to adverse events, and all withdrawals. ACR50 is defined as 50% improvement in both tender and swollen joint counts and 50% improvement in 3 of these 5 variables: patient global assessment, physician global assessments, pain scores, HAQ score, and acute-phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein]^{23,24}.

Secondary outcomes. Secondary outcomes included (1) ACR20 and ACR70²⁴; (2) changes in either DAS, a composite index of tender and swollen joint counts, patient global assessment, ESR²⁵, or DAS28 score²⁶; (3) proportion achieving a "good state", i.e., a good European League Against Rheumatism (EULAR) response^{27,28} defined by a decrease in DAS or DAS28 of ≥ 1.2 from baseline with a final DAS < 2.4 (or DAS28 < 3.2), and low disease activity defined by DAS < 2.4 or DAS28 ≤ 3.2 ; (4) quality of life, measured by Short-Form 36 (SF-36; i.e., continuous data, 8 domains, and 2 physical and mental component summary scores); (5) radiographic progression, as measured by Larsen/Sharp/modified Sharp scores²⁹⁻³¹; and (6) withdrawals due to lack of efficacy.

Safety was assessed by the type of adverse effects and SAE, including infections, serious infections, lung infections, tuberculosis, cancer, etc., and death.

Assessment of risk of bias in included studies. We independently assessed the risk of bias using 5 criteria: random sequence generation; allocation concealment: presence of patient, clinician, and assessor blinding in the studies; incomplete outcome data; and sensitive outcome reporting³². For each criterion, we assessed the risk as: Yes (low risk of bias), No (high risk of bias), or unclear (either lack of information or uncertainty over the potential for bias). Disagreements were resolved by discussion between the 2 reviewers who carried out the risk assessment. Overall rating of evidence was done by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group approach³³, in which the following ratings were used to reach a summary quality rating score: (1) high (randomized trials or double-upgraded observational studies); (2) moderate (downgraded randomized trials or upgraded observational studies); (3) low (double-downgraded randomized trials or observational studies); or (4) very low (triple-downgraded randomized trials, downgraded observational studies, or case series/case reports). The level for randomized trial evidence can be downgraded by 1 or 2 levels depending on the presence of 5 factors: serious (-1) or very serious (-2) limitations to study quality; important inconsistency (-1); some (-1) or major (-2) uncertainty about directness; imprecise or sparse data (-1); high probability of reporting bias (-1).

We calculated relative risks with 95% CI for dichotomous outcomes. For continuous measures, we calculated mean differences when possible because results presented in this form are more readily interpreted by clinicians. We performed an I-squared to quantify heterogeneity. An I-squared of 0-40% might not be important; 30%-60% may represent moderate heterogeneity; 50%-90% may represent substantial heterogeneity; and 75%-100% considerable heterogeneity³⁴. The random-effects model was the default model for pooling outcomes in the metaanalysis of studies as a conservative approach to account for clinical heterogeneity. The number needed to treat to benefit and the number needed to harm were calculated as the inverse of the absolute risk difference, using the Cates calculator³⁵.

RESULTS

Included studies and risk of bias. The initial search yielded 187 articles and the updated search an additional 29 articles (Figure 1). Of these, 4 qualified for inclusion³⁶⁻³⁹. Overall, there were 1231 patients treated with golimumab and 483

Table 1. Characteristics of patients randomized to the golimumab treatment arm at the FDA-approved dosage in included studies.

Study	Intervention Group	Comparator Drugs	Women, %	Age, Yrs, Mean (SD) or Median (IQR)	Prior MTX Failure	Prior Biologic Failure	MTX Dose, mg/wk, Mean (SD) or Median (IQR)	HAQ, Baseline, Mean (SD) or Median (IQR)	Disease Duration, Yrs, Mean (SD) or Median (IQR)	DAS28, Baseline, Mean (SD) or Median (IQR)	No. DMARD Failed, Mean (SD)
Smolen 1999 ³⁸	Golimumab + MTX	PL + MTX	74	55 (46, 63)	Yes, 67%	Yes, TNF inhibitor	— ^{††}	1.6 (1.1, 2.0)	9.6 (5.6, 17.2)	6.3 (5.6, 7.2)	— ^{††}
Kay 2009 ³⁷	Golimumab + MTX	PL + MTX	86	57 (50, 64)	Yes	No	— ^{††}	1.7 (1.4, 2.0)	8.2 (4.1, 14.3)	5.3 (4.5, 6.2)*	— ^{††}
Keystone 2009 ³⁶	Golimumab + MTX	PL + MTX	81	51 (42, 59)	Yes	No	15.0 (15.0, 20.0)	1.4 (1.0, 1.9)	4.5 (2.1, 9.7)	5.1 (4.1, 5.6)*	— ^{††}
Emery 2009 ³⁹	Golimumab + MTX	PL + MTX	85	51 (11)	No [†]	No	12.8 (2.2)	1.5 (0.7)	3.5 (5.7)	5.1 (1.0)*	— ^{††}

* Disease Activity Score 28-joint count using C-reactive protein level. [†] Half of patients were exposed to other DMARD, including but not limited to hydroxychloroquine, sulfasalazine, leflunomide, etc. ^{††} Data not provided. FDA: US Food and Drug Administration; IQR: interquartile range; MTX: methotrexate; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor.

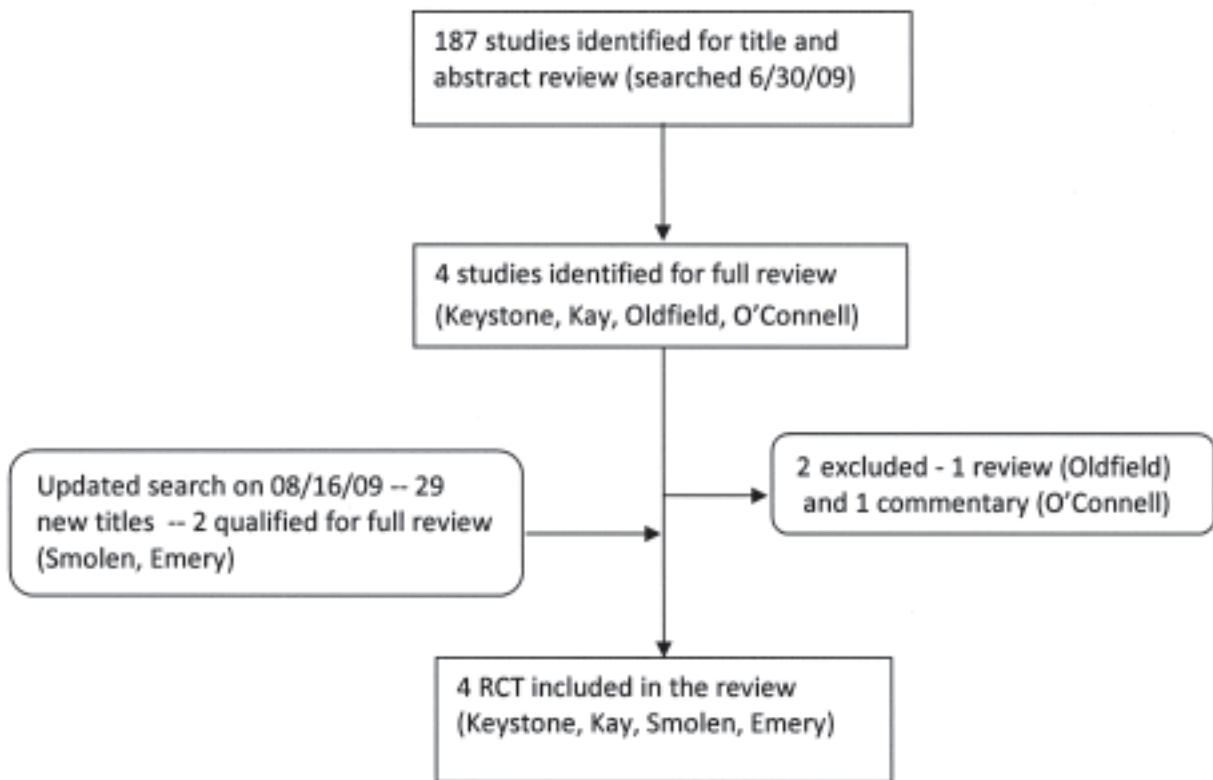


Figure 1. Selection of studies for this review. RCT: randomized controlled trial.

patients treated with placebo included in the studies, which made 1714 overall patients in all arms. There were 436 patients taking golimumab 50 mg every 4 weeks (the FDA-approved dosage); the rest of the patients taking active drugs were on other dosage schedules.

All studies reported adequate methods of randomization, allocation concealment, and blinding. The overall quality

rating of evidence was judged to be high based on the GRADE approach, with a low possibility of bias (Figure 2). *Comparison of golimumab to placebo.* Four studies³⁶⁻³⁹ provided data for ACR50. Golimumab-treated patients were 2.6 times more likely than those treated with placebo to reach ACR50 (Table 2). There was statistically significant heterogeneity with I-squared value of 76% ($p = 0.005$).

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Emery 2009	+	+	+	+	?	?
Kay 2008	+	+	+	+	?	?
Keystone 2009	+	+	+	?	?	?
Smolen 2009	+	+	+	+	?	?

Figure 2. Methodological quality summary for each study. “+”: quality standard was present; “?”: quality standard was unclear.

Golimumab-treated patients were also significantly more likely to have DAS remission, more improvement in HAQ, and lower overall withdrawal rates. While all 4 studies provided data on safety, no statistically significant differences were noted in the number of adverse events, number of SAE, or withdrawals due to adverse events.

Table 3 provides details on primary and secondary outcomes. There were no statistically significant differences between golimumab-treated patients and placebo-treated patients in the number of adverse events (absolute percentage, 73% vs 69%, $p = 0.44$), SAE (5.9% vs 5.6%, $p = 0.85$), infections (30% vs 29.5%, $p = 0.8$), serious infections (1.8% vs 1.6%, $p = 0.9$), tuberculosis reactivation (0.2% vs 0%, $p = 0.5$), lung infections (7.1% vs 7.3%, $p = 0.9$), and cancer (0.5% vs 0.6%, $p = 0.8$). No significant heterogeneity was noted for safety outcomes except for moderate-substantial heterogeneity for the number of adverse events, I-squared of 55% ($p = 0.09$).

Patients treated with golimumab were half as likely to withdraw compared to those taking a placebo (5.2% vs 10%; $p = 0.005$; Tables 2 and 3). There was no statistically significant difference between golimumab and placebo-treated patients for withdrawals due to inefficacy (1.8% vs 3.7%,

$p = 0.1$), withdrawals due to adverse events (2.8% vs 4.9%, $p = 0.2$), or number of deaths (0.2% vs 0.2%, $p = 0.99$).

Golimumab-treated patients were 1.5 times more likely to reach ACR20, 2.8 times more likely to reach ACR70, 1.5 times more likely to achieve good EULAR response, 1.6 times more likely to achieve low disease activity, and 5.1 times more likely to reach DAS remission, compared to placebo. Patients treated with golimumab had a significantly greater change in DAS28 scores, more decrease in HAQ scores, and were 1.8 times more likely to achieve a HAQ change ≥ 0.22 .

None of the studies provided data on radiographic progression. Outcomes for other dosages of golimumab versus placebo are available in the Cochrane Review⁴⁰. The results of all dosages of golimumab mirrored the ones for 50 mg of golimumab taken every 4 weeks.

Comparison of golimumab to MTX. Two studies compared 100 mg of golimumab taken every 4 weeks to MTX in MTX-naive patients³⁹ or in patients who had failed MTX³⁶. The studies involved 292 patients treated with golimumab and 293 treated with MTX. The treatment arms included 100 mg of golimumab every 4 weeks + placebo (oral) versus placebo (injections) + MTX^{36,39}. Neither study was powered to examine the differences between these arms, but only to compare 2 doses of golimumab to placebo.

There was a statistically significant greater improvement (decrease) in HAQ scores in golimumab-treated patients compared to placebo, with a mean difference of -0.12 (95% CI $-0.16, -0.08$, $p < 0.00001$; Table 4). There were no statistically significant differences between control and golimumab groups for ACR50 rates (27% vs 21%, $p = 0.24$), number of adverse events (66% vs 67%, $p = 0.7$), SAE (3% vs 5%, $p = 0.7$), infections (33% vs 29%, $p = 0.3$), serious infections (1% vs 1%, $p = 0.7$), cancers (1% vs 1%, $p = 0.8$), total withdrawals (4% vs 6%, $p = 0.5$), withdrawals due to adverse events (25% vs 3%, $p = 0.4$), and the number of deaths (0.03% vs 0%, $p = 0.5$). With 1 study providing data³⁹, there was no statistically significant difference between the number of lung infections between the golimumab and control groups (6% vs 9%, $p = 0.3$). No significant between-group differences were noted for good EULAR response, HAQ change ≥ 0.22 , and DAS remission (Table 4).

DISCUSSION

In this review of RCT of golimumab for treatment of active RA, 4 RCT of 436 patients receiving the approved (in USA, Europe, Japan, and Canada) dosage of 50 mg every 4 weeks and 483 controls were included. We found that when used with MTX for treatment of RA, golimumab at the approved dosage resulted in important benefit that was significantly better than placebo for achieving ACR20/50/70, lower DAS28 scores, RA disease remission, and improvement in physical function at 5–6 month followup. The studies were

Table 2. Summary of findings for the US Food and Drug Administration (FDA)-approved dosage of golimumab (50 mg every 4 weeks). Studies compared golimumab + MTX to placebo + MTX for RA. Patients had failed MTX therapy (and other medications in some cases).

Outcomes	Illustrative Comparative Risks (95% CI)		Relative Effect (95% CI)	No. of Participants	Quality of the Evidence (GRADE)	NNT
	Assumed Risk Placebo + MTX	Corresponding Risk* Golimumab 50 mg q4 week + MTX				
ACR50 Followup 14–24 weeks	149 per 1000	383 per 1000 (200 to 736)	RR 2.57 (1.34 to 4.94)	919 (4 studies)	high	NNTB = 5 (2,20)
DAS remission Followup 14–24 weeks	43 per 1000	220 per 1000 (72 to 673)	RR 5.12 (1.67 to 15.66)	919 (4 studies)	high	NNTB = 6 (2, 35)
HAQ scores (scale 0 to 3) Followup mean 14 weeks	Mean HAQ score in placebo was 1.6	HAQ score in intervention group was 0.2 lower (0.25 to 0.15 lower)		308 (1 study)	high	NNTB = 3 (3,4)
Adverse events Followup 14-24 weeks	693 per 1000	728 per 1000 (644 to 818)	RR 1.05 (0.93 to 1.18)	918 (4 studies)	high	NNTH = not significant
Serious adverse events Followup 14-24 weeks	56 per 1000	59 per 1000 (35 to 100)	RR 1.05 (0.62 to 1.78)	918 (4 studies)	high	NNTH = not significant
All withdrawals Followup mean 14-24 weeks	104 per 1000	52 per 1000 (32 to 84)	RR 0.5 (0.31 to 0.81)	917 (4 studies)	high	NNTH = 20 (14,51)
Withdrawals due to adverse events Followup 14-18 weeks	50 per 1000	28 per 1000 (12 to 64)	RR 0.56 (0.24 to 1.29)	599 (3 studies)	high	NNTH = not significant

* Corresponding risk based on the assumed risk in the comparison group and the relative effect of the intervention. GRADE (Grading of Recommendations Assessment, Development, and Evaluation): high quality means further research is very unlikely to change our confidence in the estimate of effect. RR: Risk ratio; NNTB or NNTH: number needed to treat to benefit or harm; MTX: methotrexate; ACR50: American College of Rheumatology 50% improvement criteria; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire.

Table 3. Efficacy and short-term safety outcomes with FDA-approved dosage of golimumab of 50 mg every 4 weeks subcutaneously. Risk ratio was calculated using Mantel-Haenszel method for all categorical measures except for HAQ scores, change in HAQ scores, and change in DAS scores (continuous outcomes); for which mean differences were calculated between golimumab and placebo groups. Significant results are in bold type.

Outcome (time of assessment)	No. Studies	No. Participants	Risk Ratio or Mean Difference (95% CI)
ACR20 (14-24 weeks)	4	919	1.53 (1.23, 1.91)
ACR50 (14-24 weeks)	4	919	2.57 (1.34, 4.94)
ACR70 (14-24 weeks)	4	919	2.80 (1.31, 5.98)
Good EULAR response (14-24 weeks)	4	919	1.47 (1.15, 1.89)
DAS low activity (14-16 weeks)	2	378	1.64 (1.15, 2.34)
DAS remission (14-24 weeks)	4	919	5.12 (1.67, 15.66)
HAQ change \geq 0.22 (14 weeks)	1	222	1.79 (1.38, 2.31)
Change in HAQ score (14 weeks)	1	222	-0.25 (-0.29, -0.21)
HAQ scores (14 weeks)	1	308	-0.20 (-0.25, -0.15)
Change in DAS28 scores (16 weeks)	1	70	-1.10 (-1.69, -0.51)
Adverse events (16-24 weeks)	4	918	1.05 (0.93, 1.18)
Serious adverse events (16-24 weeks)	4	918	1.05 (0.62, 1.78)
Infections (16-24 weeks)	4	918	1.03 (0.84, 1.25)
Serious infections (16-24 weeks)	4	918	1.06 (0.40, 2.86)
Tuberculosis (16-24 weeks)	4	918	3.04 (0.12, 74.01)
Lung infections (16-24 weeks)	2	625	0.97 (0.55, 1.70)
Cancer (16-24 weeks)	4	918	0.81 (0.16, 4.18)
All withdrawals (14-24 weeks)	4	917	0.50 (0.31, 0.81)
Withdrawals due to adverse events (14-16 weeks)	3	599	0.56 (0.24, 1.29)
Withdrawals due to inefficacy (14-16 weeks)	3	599	0.43 (0.15, 1.21)
Death (24-52 weeks)	4	917	1.02 (0.11, 9.71)

FDA: US Food and Drug Administration; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire.

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Table 4. Comparison of golimumab to methotrexate: golimumab 100 mg every 4 weeks + placebo (oral) vs placebo (injections) + methotrexate. Risk ratio was calculated using Mantel-Haenszel method for all categorical measures except for HAQ scores, change in HAQ scores, and change in DAS scores (continuous outcomes), for which mean differences were calculated between golimumab and placebo groups. Significant results are in bold type.

Outcome (time of assessment)	No. Studies	No. Participants	Risk Ratio or Mean Difference (95% CI)
ACR20 (14-24 weeks)	2	585	1.16 (0.91, 1.47)
ACR50 (14-24 weeks)	2	585	1.44 (0.78, 2.64)
ACR70 (14-24 weeks)	2	585	1.17 (0.55, 2.50)
Good EULAR response (14-24 weeks)	2	585	1.19 (0.98, 1.44)
DAS remission (14-24 weeks)	2	585	2.33 (0.62, 8.74)
HAQ change \geq 0.22 (14 weeks)	1	266	1.18 (0.88, 1.57)
Change in HAQ score (14 weeks)	1	266	-0.12 (-0.16, -0.08)
Adverse events (16-24 weeks)	2	583	0.97 (0.87, 1.09)
Serious adverse events (16-24 weeks)	2	583	0.80 (0.23, 2.77)
Infections (16-24 weeks)	2	583	1.14 (0.89, 1.45)
Serious infections (16-24 weeks)	2	583	0.76 (0.17, 3.39)
Tuberculosis (16-24 weeks)	2	583	Not estimable
Lung infections (16-24 weeks)	2	583	0.66 (0.29, 1.47)
Cancer (16-24 weeks)	2	583	0.78 (0.08, 7.17)
All withdrawals (14 weeks)	2	583	0.77 (0.37, 1.60)
Withdrawals due to adverse events (14 weeks)	2	585	0.50 (0.09, 2.68)
Withdrawals due to inefficacy (14 weeks)	2	585	0.69 (0.29, 1.66)
Death (24 weeks)	2	585	3.00 (0.12, 72.98)

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire.

too short and underpowered for comparing safety outcomes, but the risks were similar to placebo of adverse events, SAE, infections, serious infections, tuberculosis, lung infections, cancer, or death. Withdrawals for any reason averaged 5% in the golimumab group, half as frequently as in the placebo group (10%). Although not statistically significant, withdrawals due to adverse events and withdrawals due to inefficacy were also lower in the golimumab group (2.8% and 1.8%) compared with the placebo group (4.9% and 3.7%, respectively). None of the RCT were powered to have safety as a major outcome, which makes them liable to type II error, i.e., lack of differences between treatment and placebo arms may be due to lack of power to detect differences (too few patients). We are conducting an overview of all Cochrane Reviews of biologics to assess whether a much larger sample would make clinically useful estimates of harms possible. Longterm surveillance studies and RCT with safety as the primary outcome are needed to provide these important data.

The dramatic effect of the biologics upon slowing or stopping progression of radiographic joint damage is pivotal information for patients and clinicians making decisions on whether, when, and which biologic to use. Potential advantages of golimumab are less frequent administration (every 4 weeks) compared to other subcutaneous biologics for RA, including etanercept (twice weekly), adalimumab (every 2 weeks), and anakinra (every day), and the subcutaneous route of administration, which patients can do at home,

compared to IV administration in infusion units for infliximab, abatacept, and rituximab. These studies have not reported on radiographic outcomes.

Many findings in this review deserve further discussion. The ACR20/50/70 rates in the golimumab group (with MTX) in the approved dosage were 1.5–2.8 times higher than in the placebo + MTX group, and the DAS scores lower. The ACR50 rates are similar to those reported in the systematic reviews of other TNF blockers including etanercept¹¹, infliximab¹², and adalimumab¹³ and to other approved biologics for the treatment of RA, such as rituximab⁴¹ and abatacept¹⁵. Thus, in the absence of direct comparison studies, based on these data, golimumab seems to have an efficacy similar to the other biologics used for the treatment of RA. These efficacy data need to be confirmed for patients who fail current biologics, especially the TNF blockers, and who may be candidates for golimumab, since studies have shown that when one TNF blocker is not effective, another may be^{42,43}.

The improvements in functional limitation as measured by HAQ were clinically meaningful and statistically significant in golimumab-treated patients. This is important since one of the goals with effective therapy is to improve the function of patients with RA. Mean improvement in HAQ scores was 0.20–0.25. Almost twice as many golimumab-treated patients achieved the minimally clinical important change (MCID) of > 0.22 units on HAQ, compared to the placebo-treated patients. Thus, at the approved dosage, goli-

mumab seems to provide clinically meaningful improvements in function in patients with RA. Generic quality of life data have not been reported in these studies. Since these publications lag behind the original publications, we hope these data will be published in the near future.

The short-term safety for golimumab at the approved dosage of 50 mg every 4 weeks used in combination with MTX seems acceptable. The odds of withdrawals due to adverse events in golimumab-treated patients with RA compared to placebo were 0.80 (95% CI 0.26, 2.42). This is similar to the range reported for withdrawals due to adverse events with other commonly used biologics (in the range of 0.82–2.2)^{11,13,15,44,45}. Golimumab was not associated with any more risk of infections, serious infections, lung infections, tuberculosis, cancer, or death than placebo. Included RCT were short-duration studies powered for efficacy, but not safety outcomes. Longterm surveillance studies are needed to assure patients and physicians of its safety. The FDA Website warns against the risk of serious infections, invasive fungal infections, hepatitis B reactivation, malignancies, heart failure, demyelinating disease, and new-onset psoriasis. In a recently issued safety alert, the FDA also warns against the “increased risk of lymphoma and other malignancies in children and adolescents treated with TNF-blockers.”

Only 2 RCT provided the data on head-to-head subgroup comparisons of golimumab to MTX, and in 1 study, patients had already failed MTX before being randomized. The rates of ACR20/50/70, DAS remission, good EULAR response, and proportion achieving HAQ MCID were not different between these groups. The safety profile of golimumab was similar to that of MTX with regard to number of adverse events, SAE, infections, serious infections, cancer, all withdrawals, and withdrawals due to adverse events. Golimumab-treated patients achieved a significantly greater improvement in mean HAQ score than MTX-treated patients (–0.25 vs –0.13). However, these results must be interpreted with great caution since this was a subgroup analysis, only 2 RCT provided the data, and in 1 study, patients had already failed MTX before being randomized to MTX or golimumab, thereby giving an efficacy advantage to the golimumab group³⁶.

The quality of evidence found in the trials included in this review appears to be high because the studies reported adequate methods of allocation concealment, sequence generation using the interactive voice-response system, and adequate methods of blinding. Only 1 study lacked in addressing incomplete outcome data adequately³⁶. All trials were funded by the manufacturers of golimumab.

Our study had several strengths and limitations. Review of studies, bias assessment, and data abstraction were performed independently by 2 reviewers to avoid errors. We are limited in our ability to comment on outcomes not reported in the published reports, such as assessments of radiograph-

ic data or HRQOL. Short study duration and study design with efficacy (but not safety) as primary RCT outcome make analysis of safety difficult. Some studies described the number of patients with more than 1 adverse event and others, the total number of adverse events. We combined these somewhat heterogeneous outcomes to make the data and results easy to interpret.

We found high heterogeneity (moderate to substantial) in ACR50 and number of adverse events for comparison of golimumab to placebo. Heterogeneity was low for other efficacy and safety outcomes for placebo. The heterogeneity in the ACR50 estimate was primarily due to estimates of Emery, *et al*³⁹. Removal of this study decreased the heterogeneity to 0%. Heterogeneity in number of adverse events was primarily due to Smolen, *et al*³⁸. Removal of this study decreased heterogeneity to 0%. This implies that our confidence in these estimates is not as high as for the other outcomes, and these results must be interpreted with caution. On the other hand, since all estimates are in the same direction, we doubt that newer studies will change the interpretation regarding these outcomes.

FDA warnings are important when considering the risks of these medications. Many risks associated with TNF blockers as a class are also applicable to golimumab. To our knowledge there are no published metaanalyses or systematic reviews of golimumab in patients with RA. Four recently published reviews summarized results from various studies of golimumab without performing metaanalyses⁴⁶⁻⁴⁹.

The favorable safety and efficacy profile of golimumab used in combination with MTX in patients with RA offers a new treatment option to patients with active disease who have failed MTX or other biologics including anti-TNF- α biologics. Direct head-to-head comparison studies are needed between golimumab and other biologics, and between golimumab and triple therapy (MTX, sulfasalazine, and hydroxychloroquine). RCT with safety as the primary outcome and phase IV postmarketing surveillance studies are likely to provide patients and physicians with much needed longer-term safety data.

ACKNOWLEDGMENT

We thank Louise Falzon of the Cochrane Library for designing and performing the electronic search.

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