Review

Tocilizumab for Rheumatoid Arthritis: A Cochrane Systematic Review

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ABSTRACT. ***Objective.*** To compare the benefit and safety of tocilizumab to placebo in patients with rheumatoid arthritis (RA).

Methods. We searched multiple databases for published randomized or controlled clinical trials comparing benefit and safety of tocilizumab to placebo, disease-modifying antirheumatic drugs (DMARD), or other biologics. For dichotomous outcomes, we calculated the relative risk, and for continuous outcomes, the mean difference.

Results. Eight randomized controlled trials were included in this systematic review, with 3334 participants, 2233 treated with tocilizumab and 1101 controls. The US and Canadian approved dose of tocilizumab, 8 mg/kg every 4 weeks, was given to 1561 participants. In patients taking concomitant methotrexate, compared to placebo, patients treated with approved dose of tocilizumab were substantially and statistically significantly more likely than placebo to achieve the American College of Rheumatology 50 (absolute percentage, 38.8% vs 9.6%, respectively; RR 3.2, 95% CI 2.7, 3.7); Disease Activity Score remission (30.5% vs 2.7%; RR 8.7, 95% CI 6.3, 11.8); and a clinically meaningful decrease in Health Assessment Questionnaire (HAQ)/Modified HAQ scores (60.5% vs 34%; RR 1.8, 95% CI 1.6, 1.9). There were no substantive statistically significant differences in serious adverse effects (0.8% vs 0.7%; RR 1.2, 95% CI 0.8, 1.6) or withdrawals due to adverse events (4.9% vs 3.7%; RR 1.4, 95% CI 0.9, 2.1); however, tocilizumab-treated patients were significantly more likely to have any adverse event (74% vs 65%; RR 1.05, 95% CI 1.03, 1.07); elevation in the ratio of low-density lipoprotein to high-density lipoprotein cholesterol (HDL; 20% vs 12%; RR 1.7, 95% CI 1.2, 2.2); and increase in the ratio of total to HDL cholesterol (12% vs 7%; RR 1.7, 95% CI 1.2, 2.6); and they were less likely to withdraw from treatment for any reason (8.1% vs 14.9%; RR 0.6, 95% CI 0.5, 0.8).

Conclusion. At the approved dose of 8 mg/kg every 4 weeks, tocilizumab in combination with methotrexate/DMARD is beneficial in decreasing RA disease activity and improving function. Tocilizumab treatment was associated with a significant increase in cholesterol levels and occurrence of any adverse event, but not serious adverse events. Larger safety studies are needed to address these safety concerns. (J Rheumatol First Release Oct 15 2010; doi:10.3899/jrheum.100717)

Key Indexing Terms:
TOCILIZUMAB RHEUMATOID ARTHRITIS BENEFIT SAFETY

Rheumatoid arthritis (RA) is a chronic, multisystem autoimmune disease that is characterized by inflammation of synovium in the joints and tendons and other systemic manifestations. RA affects 0.5%–1% of the general popula-

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tion, with most patients presenting in their productive years, usually in the third or fourth decade of life[1]. RA leads to significant pain and decrements in the quality of life, a decline in functional status, and progressive disability[2,3,4]. Currently, there are numerous treatment options available to patients with RA. However, the therapeutic failure rate remains moderate and thus new interventions are still required and constantly researched.

Current interventions for RA include nonsteroidal anti-inflammatory drugs (NSAID), disease-modifying anti-rheumatic drugs (DMARD) such as methotrexate, and newer biologic DMARD. The biologic DMARD target cytokines such as tumor necrosis factor (TNF) and interleukins, which play an important role in joint inflammation and destruction, the hallmark of RA. One such target is interleukin 6 (IL-6), which contributes to the pathogenesis of RA by promoting the activation of T cells and the differentiation of B cells into immunoglobulin-secreting plasma cells[5]. Recently, tocilizumab, an antibody that targets IL-6 receptors, has been introduced for treatment of RA[5]. Tocilizumab has been approved for use in the United States, Canada, Japan, Switzerland, India, Brazil, Kuwait, Peru, Moldova, Liechtenstein, and the European Union[6,7,8]. The objective of this Cochrane systematic review was to assess benefit and safety of tocilizumab based on randomized controlled trial (RCT) data.

MATERIALS AND METHODS

Types of studies and participants. Inclusion criteria for trials were published randomized or quasirandomized (methods of allocating participants to a treatment that are not strictly random, e.g., date of birth, hospital record number, or alternation) clinical trials comparing tocilizumab alone or in combination with DMARD or biologics to placebo and/or DMARD and/or biologics for treatment of adults (age 18 years or older) with RA who met the 1987 American College of Rheumatology (ACR) classification criteria for RA[9]. There were no restrictions with regard to dosage or duration of intervention. An expert librarian searched the following databases (Appendix): (1) The Cochrane Central Register of Controlled Trials, through The Cochrane Library, Wiley InterScience (www.thecochranelibrary.com), issue 3, 2009; (2) OVID Medline, 1966-October 1, 2009; (3) CINAHL (via EBSCOHost), 1982-2009, week 39; (4) EMBASE 1980-2009; (5) Science Citation Index (Web of Science) 1945-2009; and (6) Current Controlled Trials. All titles and abstracts were screened for inclusion by 2 review authors.

Types of outcome measures. Seven major outcomes were chosen *a priori* in accordance with the Cochrane Musculoskeletal Group's guidelines. Outcomes assessing benefit were (1) ACR50[10], defined as 50% improvement in both tender and swollen joint counts and 50% improvement in 3 of the following 5 variables: patient's global assessment, physician's global assessments, pain scores, Health Assessment Questionnaire (HAQ) score, and acute-phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)][10,11]; (2) Disease Activity Score (DAS), DAS remission (DAS < 1.6 or DAS28 < 2.6); (3) function measured by HAQ score or modified HAQ calculated as score changes[12,13], the proportion achieving minimal clinically important difference (MCID) on HAQ ≥ 0.22[14]; (4) quality of life, measured by Short-Form 36 (SF-36; i.e., continuous data, 8 domains, and physical and mental component summary scores); and (5) radiographic progression as measured by Larsen, Sharp, or modified Sharp scores[15,16,17].

Two safety measures were the number of serious adverse events, and the number of withdrawals due to adverse events.

Secondary outcomes included (1) ACR20 and ACR70, defined as 20% and 70% improvement in variables under the primary outcome[10]; (2) changes in either DAS, a composite index of tender and swollen joint counts, patient global assessment, and ESR[18], or DAS28 score[19]; (3) proportion achieving a "good state": (a) good European League Against Rheumatism (EULAR) response[20,21] defined by a decrease in DAS or DAS28 of ≥ 1.2 from baseline with a final DAS < 2.4 (or DAS28 < 3.2); (b) low disease activity defined by DAS < 2.4 or DAS28 ≤ 3.2; (4) quality of life, measured by SF-36 (i.e., continuous data, 8 domains; and physical and mental component summary scores); (5) all withdrawals; (6) withdrawals due to lack of benefit; and (7) safety as assessed by the number and types of adverse events (AE) and types of serious adverse events (SAE), including infections, serious infections, lung infections, tuberculosis, and cancer.

Search methods for identification of studies. Two review authors independently extracted data from the included trials, including information on population of study, number of centers, types of intervention, primary and secondary outcomes, and analyses performed in the original studies. The data were gathered using standardized extraction methods. Data entered into datasheets were verified by the senior author by comparison to original studies[22].

Assessment of risk of bias. In order to assess the risk of bias in the included studies, 2 review authors independently examined the studies using the Cochrane Collaboration recommendations of assessing risk of bias, paying particular attention to the presence of blinding in the studies (of participants, caregivers, and outcome assessors), allocation concealment, random sequence generation, incomplete outcome data, and selective outcome reporting[23].

Overall rating of evidence was done using the GRADE approach[24] with the following ratings 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, or downgraded observational studies, or case series/case reports.

Statistical analyses. For benefit and safety, we calculated relative risk for dichotomous and mean differences for continuous outcomes. In the case of rare events (such as death, etc.), risk difference was calculated using the Mantel-Haenszel test, and 95% CI were calculated. We determined heterogeneity by calculating the I-squared (I^2), which is interpreted as the proportion of total variation among effect estimates that is due to heterogeneity. I^2 is intrinsically independent of the number of studies and an I^2 statistic of greater than 50% may represent substantial heterogeneity[25]. If substantial heterogeneity was detected, we used random effects models instead of fixed effects and tried to analyze it using subgroup analyses.

Absolute risk difference was defined as the difference between risk in the treatment group and risk in the control group. The inverse of the absolute risk difference was used to calculate the number needed to treat to benefit and for harm, the number needed to treat to harm, using the Cates calculator Visual Rx[26].

The following subgroup analyses were planned *a priori*: (1) concomitant methotrexate versus no methotrexate; (2) mean RA disease duration, categorized as early RA, defined as duration < 2 years[27] versus established RA, duration 2 to 10 years, versus late RA, defined as > 10 years[28,29]; (3) use in patients who have methotrexate failure versus biologic failure; (4) DMARD-naive versus not naive; (5) single biologic DMARD agent versus combination biologic therapy; and (6) treatment duration with biologic or DMARD: short (6 months), intermediate (6 to 12 months), or long duration (> 1 year).

RESULTS

The initial search in June 2009 retrieved 409 results. Of

these 409, we identified 22 studies for full review (Figure 1). Of those 22 studies, 8 qualified for inclusion: Choy 2002[30], Emery 2008 (RADIATE)[31], Genovese 2008 (TOWARD)[32], Maini 2006 (CHARISMA)[33], Nishimoto 2004[34], Nishimoto 2007 (SAMURAI)[35], Nishimoto 2009 (SATORI)[36], and Smolen 2008 (OPTION)[37]. A search update performed in October 2009 yielded 47 new results; none qualified for inclusion. The key characteristics of included studies are summarized in Table 1. The total number of participants was 3334, out of which 2233 were treated with tocilizumab and 1101 served as controls. Patients treated with tocilizumab alone numbered 939; 489 patients were treated with a combination of tocilizumab and methotrexate and 805 were treated with tocilizumab plus DMARD.

All the trials were reported as multicenter trials and included adults aged ≥ 18 years meeting the ACR criteria for RA. In all the included trials, participants had active disease (as defined by ACR revised criteria) of ≥ 6 months' duration. Average RA disease duration ranged from 7 to 13 years, except 2.4 years in Nishimoto 2007[35] and 0.6–53 years in Nishimoto 2004[34]. In 7 RCT, patients had unsuccessful treatment with methotrexate and/or other DMARD[30,32,33,34,35,36,37]; Emery 2008 included patients who failed TNF antagonists (with or without traditional DMARD)[31]. RCT duration ranged from 8 weeks for Choy 2002[30] to 52 weeks for Nishimoto 2007[35].

Risk of bias in included studies (Figure 2). Adequate allocation concealment was described in 2 trials, Maini 2006[33] and Smolen 2008[37]. Central randomization for sequence generation was reported by Maini 2006[33], Nishimoto 2007[35], and Nishimoto 2009[36]. All the trials except Nishimoto 2007[35] were reported as double-blind. All the studies except Nishimoto 2004[34] reported an intent-to-treat analysis for the primary outcome. Manufacturers of tocilizumab played a role in sponsoring the study drugs, sponsoring the study, providing research grants to authors of the studies, and/or participating in components of the study.

Tocilizumb 8 mg/kg plus methotrexate/DMARD (tocilizumb group) versus placebo + methotrexate/DMARD (control group). Four studies provided these data: Genovese 2008[32], Smolen 2008[37], Emery 2008[31], and Maini 2006[33]. Seven key outcomes are shown in Table 2; additional outcomes are summarized in Table 3. The tocilizumab group was 3.2 times more likely to achieve ACR50, 8.7 times more likely to achieve DAS remission, and 1.8 times more likely to achieve minimal clinically important improvement in HAQ/MHAQ scores, compared to the control group. None of the studies provided data on radiographic progression, comparing tocilizumab in combination with methotrexate/DMARD versus placebo in combination with methotrexate/DMARD. Tocilizumab group subjects were less likely to withdraw for any reason compared to the control group (0.6 times). No statistically significant difference was noted in the total number of SAE and withdrawals due to AE.

As far as secondary outcomes, tocilizumab group patients were 2.5 times more likely to achieve ACR20 and 6

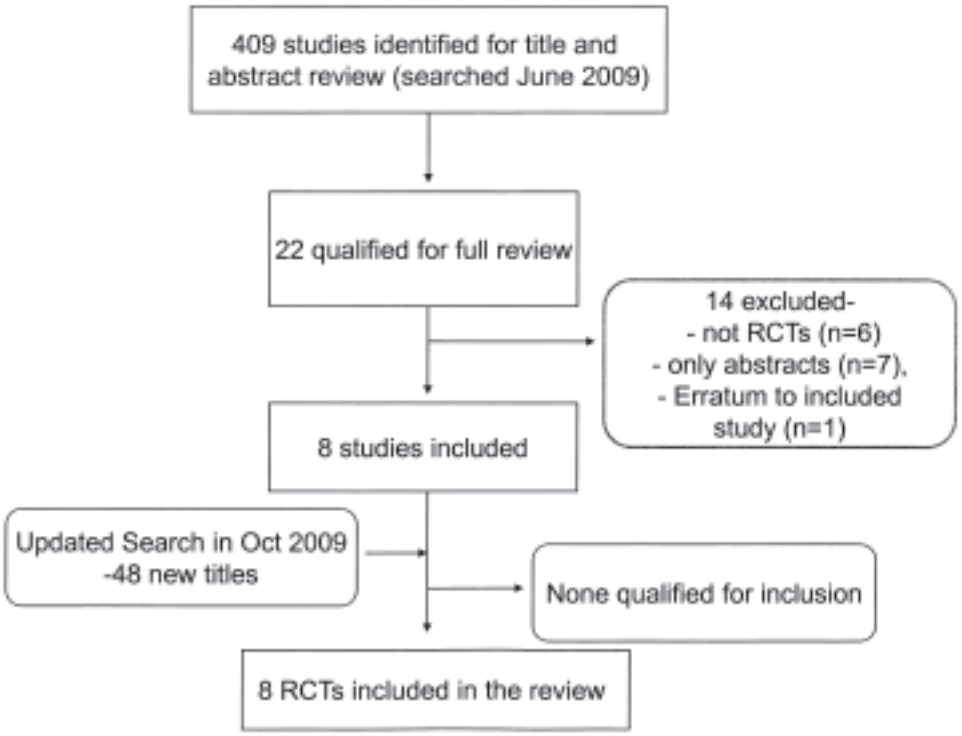

Figure 1. Study selection pattern. RCT: randomized controlled trial.

Table 1. Characteristics of randomized controlled trials of tocilizumab in rheumatoid arthritis.

Study	Intervention Group Drugs	Comparator	Women, %	Age, yrs, mean (SD); median [range]	Prior MTX Failure	Prior Biologic Failure (yes, no)	MTX, mg/wk, mean (SD) (yes, no)	Baseline HAQ, mean (SD)	Baseline DAS, mean (SD)	Baseline DAS28, mean (SD)	RA Duration, yrs (SD)	No. DMARD Failed, mean (SD) [range]
Nishimoto 2009	TCZ + PL	MTX + PL	90	52.6 (10.6)	Yes	No	NR	NR	NR	6.1 (0.9)	8.5 (8.4)	3.3 [1–8]
Nishimoto 2007	TCZ	Conventional DMARD	80	52.9 (11.6)	NR; failed at least 1 DMARD	No	6.9 (2.0)	NR	NR	6.5 (0.8)	2.2 (1.4)	2.7 ([1–7]
Nishimoto 2004[a]	TCZ	PL	84	Median 56 [21–74]	NR; failed at least 1 DMARD	No	NR	NR	NR	NR	Median 8.3 [1.3–46]	Median 5 [1–11]
Maini 2006[a]	TCZ or TCZ + MTX	MTX + PL	73	50.1 (NR)	Yes	No	NR[d]	NR	NR	6.4 (NR)	9.2 (NR)	NR
Choy 2002[c]	TCZ	PL	71	61.5 (7.8)	NR but failed at least 1 DMARD	No	NR	NR	NR	NR	13 (11)	3 (2)
Emery 2008[b]	TCZ + MTX	PL + MTX	80	53.9 (12.7)	No	Yes	15.7 (4.4)	1.7 (0.6)	NR	6.79 (0.93)	12.6 (9.3)	NR
Genovese 2008	TCZ + DMARD	PL + DMARD	81	53 (11)	NR but failed at least 1 DMARD	No	14.7 (NR)	1.5 (0.6)	NR	6.7 (1.0)	9.8 (8.8)	NR
Smolen 2008[b]	TCZ + MTX	PL + MTX	85	50.8 (11.8)	Yes	No	14.5 (4.4)	1.6 (0.6)	NR	6.8 (0.9)	7.5 (7.3)	NR

TCZ: tocilizumab; MTX: methotrexate; HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; DAS28: 28-joint DAS; RA: rheumatoid arthritis; PL: placebo; NR: not reported; DMARD: disease-modifying antirheumatic drug. [a] Data pertain to patients who received TCZ 8 mg/kg (monotherapy); [b] patients who received TCZ 8 mg/kg (plus MTX); [c] patients who received TCZ 10 mg/kg; [d] not provided, only categorization of patients in low, medium, and high-dose groups.

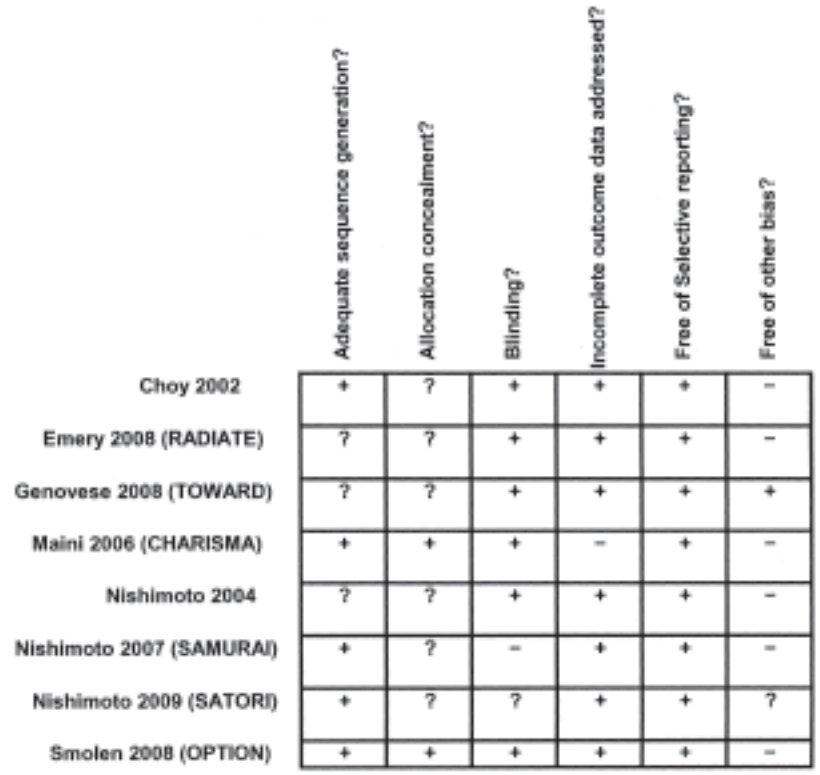

Figure 2. Assessment of risk bias. + indicates Yes (low risk of bias); ? indicates the risk of bias is unclear; – indicates No (high risk of bias). For Nishimoto 2007, only radiograph readers were blinded to the treatment group, the chronological order of the radiographs, and the clinical response of each patient. For Maini 2006, the reported number for withdrawals did not add up to the percentage of patients completing the study. For other bias, most studies had investigators who had received honoraria from the makers of tocilizumab. All studies were funded by the maker of tocilizumab. RCT: randomized controlled trial.

Table 2. Summary of findings for 7 key outcomes comparing tocilizumab to placebo for rheumatoid arthritis (RA). Patient or population: Patients with RA. Intervention: tocilizumab 8 mg/kg + MTX/DMARD vs placebo + MTX/DMARD. The corresponding risk (95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention. Ratings for the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group: High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate.

Outcomes	Illustrative Comparative Risks (95% CI)		Relative Effect (95% CI)	No. of Participants (studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk Control	Corresponding Risk TCZ 8 mg/kg + MTX/DMARD vs placebo + MTX/DMARD				
ACR50% improvement criteria Followup: mean 16–24 wks	95 per 1000	301 per 1000 (258 to 349)	RR 3.17 (2.72 to 3.67)	2063 (4 studies)	High[1]	Absolute risk difference 29% (25%, 32%); relative risk difference 217% (172%, 267%); NNTB 5 (4, 6)
DAS remission defined as DAS28 < 2.6 Followup: mean 16–24 wks	28 per 1000	245 per 1000 (175 to 330)	RR 8.74 (6.26 to 11.8)	1946 (4 studies)	High[1]	Absolute risk difference 27% (24%, 30%); relative risk difference 774% (526%, 1080%); NNTB 5 (3, 7)
HAQ improvement of > 0.3 or MHAQ decrease of > 0.22 (changes exceeding MCID) Followup: mean 24 wks	340 per 1000	609 per 1000 (551 to 660)	RR 1.79 (1.62 to 1.94)	1220 (1 study)	High[1]	Absolute risk difference 26% (20%, 32%); relative risk difference 79% (62%, 94%); NNTB 4 (3, 5)
Radiographic Progression	See comment	See comment	Not estimable	0 (0[4])	See comment	See comment
Serious adverse events Followup: mean 24 wks	67 per 1000	78 per 1000 (56 to 110)	RR 1.17 (0.83 to 1.64)	1961 (3 studies)	Moderate[1,2]	Absolute risk difference 0% (–5%, 5%); relative risk difference 17% (–0.17%, 64%); NNTH not applicable[3]
Total withdrawals Followup: mean 16–24 wks	123 per 1000	75 per 1000 (60 to 95)	RR 0.61 (0.49 to 0.77)	2064 (4 studies)	Moderate[1,2]	Absolute risk difference –4% (–9%, –1%); relative risk difference –39% (–51%, –23%); NNTH 21 (16, 35)
Withdrawals due to adverse events Followup: mean 16–24 wks	36 per 1000	51 per 1000 (24 to 76)	RR 1.43 (0.95 to 2.12)	2064 (4 studies)	High[1]	Absolute risk difference 2% (–0%, 4%); relative risk difference 43% (–5%, 122%); NNTH not applicable[3]

[1] Allocation concealment is not reported by many included studies. Allocation sequence generation was unclear in some studies as well. [2] There was a high heterogeneity with an overall I^2 of 71% for total number of serious adverse events and 63% for total withdrawals. [3] Number needed to treat is not applicable, since the relative risk included 1 and the rate for tocilizumab was not significantly different from placebo. [4] There were no studies comparing radiographic progression between tocilizumab + methotrexate/DMARD vs placebo + MTX/DMARD. However, 1 study at US-approved doses without MTX in either arm, i.e., tocilizumab vs MTX/DMARD as the control arm (Nishimoto 2007), showed that tocilizumab-treated patients were 1.45 times more likely to show no radiographic progression [change from baseline in the Total Sharp Score (TSS) ≤ 0.05] compared to the control group ($p < 0.01$). TSS were 3.8 lower and erosion scores were 2.3 lower in the tocilizumab group compared to the control group. Joint space narrowing scores were 1.4 lower in the tocilizumab group ($p < 0.05$). MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; DAS: Disease Activity Score; DAS28: 28-joint DAS; HAQ: Health Assessment Questionnaire; MHAQ: modified HAQ: NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm; MCID: minimal clinically important difference.

times more likely to achieve ACR70 compared to the control group. The tocilizumab group showed significantly better DAS28 scores ($p < 0.0001$) and significantly greater improvements in DAS28 scores (2-unit difference), HAQ scores (0.3-unit difference), Functional Assessment of Chronic Illness Therapy scores (a measure of fatigue; 4.4-unit difference), SF-36 physical component summary (4.7-unit difference), and SF-36 mental component summary scores (3.4-unit difference). Tocilizumab-treated patients were 13 times more likely to achieve a good EULAR response compared to the control group.

Several AE were significantly more common in tocilizumab compared to the placebo group. Tocilizumab group subjects were more likely to develop any AE (1.1 times), gastrointestinal disorders (1.5 times), rash (4 times), 30% elevation of the ratio of low-density lipoprotein (LDL)

Table 3. Secondary efficacy and safety outcomes of the approved 8 mg/kg dose of tocilizumab with concomitant methotrexate/DMARD compared with placebo + methotrexate/DMARD.

Outcome (Time of Assessment)	No. Studies	No. Participants	Risk Ratio or Mean Difference[a,b] (95% CI)
ACR20 (16–24 wks)	4	2063	2.53 (1.88, 3.39)
ACR70 (16–24 wks)	4	2063	5.94 (2.83, 12.48)
Good EULAR response (24 wks)	1	409	12.94 (5.77, 29.01)
DAS28 Score (16–24 wks)	3	1728	–2.00 (–2.10, –1.91)
DAS low disease activity (16 wks)	3	1680	8.62 (6.22, 11.94)
HAQ scores (24 wks)	3	1964	–0.29 (–0.34, –0.23)
SF-36 physical component summary (24 wks)	2	1628	4.72 (4.01, 5.43)
SF-36 mental component summary (24 wks)	2	1628	3.44 (2.34, 4.54)
FACIT fatigue score (24 wks)	2	1628	4.46 (3.35, 5.56)
Any adverse event (AE)	4	2060	1.14 (1.07, 1.21)
Patients with at least 1 serious AE (16–24 wks)	3	1725	1.50 (0.99, 2.25)
Decrease in neutrophil counts from normal to low (24 wks)	1	1216	7.11 (4.41, 11.46)
Increase of 30% in LDL:HDL ratio (24 wks)[c]	1	1220	1.66 (1.24, 2.23)
Increase of 30% in total:HDL cholesterol ratio (24 wks)[c]	1	1220	1.72 (1.16, 2.57)
Upper respiratory infections (24 wks)	1	410	1.29 (0.65, 2.60)
Infections (24 wks)	3	1961	1.18 (1.04, 1.34)
Serious infections and infestations (16–24 wks)	4	2060	1.80 (0.98, 3.32)
Any gastrointestinal disorder (24 wks)	3	1961	1.42 (1.18, 1.71)
Rash (24 wks)	1	410	3.63 (1.03, 12.82)
Withdrawals due to inefficacy (16–24 wks)	4	2064	0.28 (0.19, 0.43)
Death (24 wks)	2	1551	0.52 (0.07, 3.65)

[a] Risk ratio calculated using Mantel-Haenszel method for all categorical measures except HAQ scores, change in HAQ scores, and change in DAS scores (continuous outcomes), for which mean differences were calculated between golimumab and placebo groups. [b] For rare events or when counts were zero, risk difference uses the Mantel-Haenszel method. [c] 30% change in ratio was reported in the study, but no explanation was provided for the choice of the 30% value. DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DAS: Disease Activity Score; DAS28: 28-joint DAS; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short-Form 36 questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol.

to high-density lipoprotein (HDL) cholesterol (1.7 times), 30% increase in the ratio of total:HDL cholesterol (1.7 times), and a drop in neutrophil count from normal at baseline to low at followup (7.1 times). No differences were noted in deaths, SAE, or upper respiratory infections.

Tocilizumab 8 mg/kg plus placebo versus placebo plus methotrexate. Three studies provided data — Maini 2006[33], Nishimoto 2007[35], and Nishimoto 2009[36]. Tocilizumab was significantly better than methotrexate in achieving ACR20 and ACR50 (but not ACR70), lower DAS28 scores, DAS remission, HAQ improvement exceeding MCID, lower Sharp score, and slowing radiographic progression at 1 year (Table 4). Tocilizumab-treated patients were 1.45 times as likely to achieve no radiographic progression [defined as Total Sharp Score (TSS) change ≤ 0.5] compared to placebo. This translated into number needed to treat to benefit of 6 (95% CI 3 to 20). Compared to methotrexate, tocilizumab was significantly more likely to be associated with any AE, rash, paronychia, increase in total and LDL cholesterol, and increase in triglycerides. Total withdrawals, those due to lack of benefit or AE, were not different between groups.

Data from other comparisons of 8 mg/kg dose to placebo and with other tocilizumab doses are described in the Cochrane Review[22].

A priori specified subgroup analyses: ACR 20/50/70. Two subgroup analyses (DMARD-naive vs not naive and single vs multiple biologic) could not be performed because of absence of data.

1. Concomitant methotrexate versus no methotrexate: Tocilizumab was significantly better than placebo in achieving ACR20 both in those with and those without concomitant methotrexate. ACR50 and ACR70 rates were slightly higher in patients with concomitant methotrexate than in those without methotrexate (Table 5).
2. Mean RA disease duration: There were no studies with mean RA disease duration less than 2 years. ACR20/50/70 rates seemed higher with tocilizumab as compared to placebo in patients with RA with > 10 years of disease than in patients with 2–10 years of disease duration (Table 5).
3. Use in patients who have methotrexate failure versus biologic failure: Tocilizumab was more effective than placebo in those who had failed biologics than in patients who had

Table 4. Comparison of tocilizumab to methotrexate: tocilizumab 8 mg/kg every 4 weeks + placebo (oral) vs placebo (injections) + methotrexate. Risk ratio calculated using Mantel-Haenszel method for all categorical measures except HAQ scores, change in HAQ scores, and change in DAS scores (continuous outcomes), for which mean difference were calculated between golimumab and placebo groups. For rare events or when counts were zero, risk difference uses the Mantel-Haenszel method.

Outcome (Time of Assessment)	No. Studies	No. Participants	RR or Mean Difference (95% CI)
ACR20 (16–52 wks)	3	528	2.25 (1.58, 3.20)
ACR50 (16–52 wks)	3	528	3.14 (1.35, 7.28)
ACR70 (16–52 wks)	3	528	2.31 (0.32, 16.66)
DAS remission (16–52 wks)	3	528	11.84 (5.88, 23.85)
DAS28 score (16–52 wks)	3	528	–2.29 (–3.33, –1.25)
MHAQ change ≥ 0.22 (16–52 wks)	2	427	1.77 (1.46, 2.15)
No radiographic progression (score < 0.5; 52 wks)	1	302	1.45 (1.13, 1.86)
Total Sharp Score (52 wks)	1	300	–3.80 (–4.53, –3.07)
≥ 1 adverse events (16–52 wks)	3	528	1.15 (1.06, 1.26)
Serious adverse events (16–52 wks)	3	528	1.37 (0.84, 2.22)
Rash (52 wks)	2	427	2.49 (1.13, 5.51)
Paronychia (52 wks)	1	302	8.31 (1.07, 64.80)
Infusion reactions/anaphylactic reactions (16–52 wks)	2	403	0.05 (0.02, 0.09)
Cancer (52 wks)	1	302	6.93 (0.71, 67.29)
Increase in total cholesterol (52 wks)	1	302	111.81 (6.98, 1791.72)
Increase in triglycerides (52 wks)	1	302	8.21 (3.73, 18.09)
Increase in LDL cholesterol (52 wks)	1	302	9.19 (4.76, 17.75)
All withdrawals (16–52 wks)	2	427	0.61 (0.10, 3.76)
Withdrawals due to adverse events (16–52 wks)	2	427	2.26 (1.00, 5.09)
Withdrawals due to inefficacy (16–52 wks)	1	302	0.62 (0.22, 1.69)

ACR: American College of Rheumatology; DAS: Disease Activity Score; DAS28: 28-joint DAS; HAQ: Health Assessment Questionnaire; MHAQ: modified HAQ: LDL: low-density lipoprotein.

failed methotrexate (Table 5). This seemed to be due to very low response rates in the placebo group of the single study that recruited patients who had failed biologics.

4. Treatment duration with tocilizumab: Treatment effect of tocilizumab versus placebo was slightly more pronounced for study duration of 6–12 months (5–9 times) than for study duration ≤ 6 months (2–4 times; Table 5).

DISCUSSION

In this systematic review, we analyzed evidence from 8 RCT of tocilizumab for patients with RA. Tocilizumab was beneficial in decreasing disease activity and improving function and quality of life of patients with RA, in all doses including the approved dose. The benefit was noted in comparison to placebo with and without concomitant methotrexate, although it was more pronounced with concomitant methotrexate. AE including elevation of cholesterol, infections, and any gastrointestinal disorder were higher than placebo, but the number of SAE, deaths, and withdrawals due to AE did not differ between tocilizumab and placebo. Compared to methotrexate, tocilizumab was more effective for several clinical outcomes including ACR20 and ACR50 (but not ACR70), DAS remission, and HAQ improvement, but was also associated with more toxicity. With limitations of sample size, short followup, and lack of safety outcomes as primary outcomes in RCT, tocilizumab appeared to be relatively safe. Tocilizumab is approved at the 8 mg/kg dosage every 4 weeks in many countries and regions.

Several observations deserve further discussion. Compared to placebo, patients treated with the approved dose of tocilizumab were 3.2 times more likely than placebo to achieve ACR50 (absolute percentage, 39% vs 10%, respectively) and 8.7 times more likely to achieve DAS remission (31% vs 3%). There are no head-to-head RCT of tocilizumab and other biologics in patients with RA. In the absence of direct comparisons, the benefit of tocilizumab seems to be similar to other approved biologics for treatment of RA including etanercept[38], infliximab[39], adalimumab[40], golimumab[41], rituximab[42], and abatacept[43], and better than anakinra[44]. The frequency of administration (monthly) and the subcutaneous injection route make it a reasonable option for patients with RA. In these RCT, the quality of life and function improvements with tocilizumab exceeded those with placebo significantly. Tocilizumab-treated patients had less radiographic disease progression compared to methotrexate in one 52-week study. Although radiographic data were reported in only 1 study, the inhibition of radiographic progression with tocilizumab is consistent with other biologics. A recent study found that a 1-unit change on TSS corresponds to a 0.01-unit change in HAQ score, linking functional limitation to radiographic damage[45]. Tocilizumab-treated patients had HAQ score change of

Table 5. A priori subgroup analyses comparing ACR 20/50/70 rates in tocilizumab compared to placebo.

Outcome (Time of Assessment)	No. Studies	No. Participants	RR or Mean Difference (95% CI)
ACR20	7	3288	2.45 (2.20, 2.74)
Concomitant MTX	5	2824	2.37 (2.10, 2.68)
No concomitant MTX	2	464	2.82 (2.21, 3.60)
ACR50	7	3258	3.40 (2.89, 4.01)
Concomitant MTX	5	2794	3.72 (3.03, 4.56)
No concomitant MTX	2	464	2.71 (2.10, 3.49)
ACR70	7	3288	3.63 (2.92, 4.50)
Concomitant MTX	5	2824	4.92 (3.47, 6.97)
No concomitant MTX	2	464	2.55 (1.99, 3.27)
ACR20	7	3288	2.13 (1.92, 2.37)
< 2 yr RA disease duration	0	0	Not estimable
2–10 yr RA disease duration	6	2790	2.01 (1.81, 2.25)
> 10 yr RA disease duration	1	498	4.08 (2.52, 6.61)
ACR50	7	3288	3.30 (2.80, 3.89)
< 2 yr RA disease duration	0	0	Not estimable
2–10 yr RA disease duration	6	2790	3.16 (2.68, 3.73)
> 10 yr RA disease duration	1	498	6.07 (2.70, 13.64)
ACR70	7	3288	5.49 (4.04, 7.46)
< 2 yr RA disease duration	0	0	Not estimable
2–10 yr RA disease duration	6	2790	5.40 (3.95, 7.39)
> 10 yr RA disease duration	1	498	7.10 (1.72, 29.35)
ACR20	7	3113	2.34 (2.09, 2.62)
MTX failure	6	1893	2.35 (1.87, 2.95)
Biologic failure	1	1220	4.05 (2.50, 6.57)
ACR50	7	3288	3.80 (2.37, 6.10)
MTX failure	6	2068	3.56 (2.13, 5.95)
Biologic failure	1	1220	6.07 (2.70, 13.64)
ACR70	7	3288	5.03 (2.32, 10.91)
MTX failure	6	2068	4.83 (2.05, 11.40)
Biologic failure	1	1220	7.10 (1.72, 29.35)
ACR20	7	3288	2.45 (2.20, 2.74)
≤ 6 mo RCT duration	2	521	2.31 (1.67, 3.19)
> 6–12 mo RCT duration	5	2767	2.47 (2.20, 2.78)
ACR50	7	3288	3.89 (3.23, 4.68)
≤ 6 mo RCT duration	2	521	2.00 (1.27, 3.16)
> 6–12 mo RCT duration	5	2767	4.32 (3.52, 5.29)
ACR70	7	3288	5.49 (4.04, 7.46)
≤ 6 mo RCT duration	2	521	1.76 (0.93, 3.33)
> 6–12 mo RCT duration	5	2767	6.89 (4.83, 9.84)

ACR: American College of Rheumatology; RA: rheumatoid arthritis; RCT: randomized controlled trial; MTX: methotrexate.

–0.29 more than placebo, which would equate to about 30 points less progression on TSS.

The overall safety of tocilizumab seems acceptable, given the limitation of short-term duration and the lack of adequate power to detect differences in safety outcomes. At the approved dose, the risk of any AE was significantly higher in tocilizumab-treated patients compared to placebo (absolute percentage, 74% vs 65%, respectively; RR of 1.15). SAE (8% vs 7%) and withdrawals due to AE (5% vs 4%) were similar between the groups. In addition to the risk of gastrointestinal problems and rash, an increase in cholesterol levels was also noted in studies. More studies are needed with safety as the primary outcome to better define these risks.

Tocilizumab is the first biologic targeting IL-6 that is approved for the treatment of moderate to severe active RA. With future advances in pharmacogenomics, biologics targeting different cytokines may offer unique options for personalized medicine for patients with RA.

We found that the quality of evidence for tocilizumab was high for 5 of the 7 summary of findings outcomes, because the studies reported adequate methods of blinding, followup, and outcome reporting, with consistent estimates for most outcomes. Significant heterogeneity was noted for only 2 outcomes, the number of SAE and withdrawals due to safety, which led to moderate-quality evidence for these outcomes. Specifically, allocation concealment was not reported by many included studies. Allocation sequence generation was unclear in some studies as well.

Two reviewers independently reviewed all abstracts and titles, abstracted data, and performed bias and quality assessments. Therefore, errors in abstraction are minimized. The protocol for the review was developed and published *a priori*.

Our study has several limitations. Analyses of safety outcomes are somewhat limited, since most studies are designed primarily for benefit outcomes. Lack of differences in the safety outcomes may be due either to lack of power to detect differences or lack of difference in these outcomes. We do not have access to unpublished data; availability of more studies may change interpretation of results.

Tocilizumab is the first biologic used for the treatment of RA that inhibits IL-6. Based on the benefit data, it seems to have benefits comparable to the other biologics currently approved for the treatment of RA. Tocilizumab retards radiographic progression in RA. Thus, tocilizumab is a potential therapeutic option for patients with active RA who have failed current therapies including methotrexate and in some cases anti-TNF biologics. The 4-weekly regimen and administration make it an attractive option for patients who desire less frequent injections. There are several safety concerns with tocilizumab that need further and continued study, including infections and changes in cholesterol levels.

ACKNOWLEDGMENT

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APPENDIX: Search strategy.

Ovid Medline in-process and other non-indexed citations, Ovid Medline daily and Ovid Medline 2005 to June Week 3, 2009

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. bechterew$ disease.tw.
9. or/1-8
10. exp Receptors, Interleukin-6/
11. Interleukin-6/
12. Tocilizum$.af.
13. altizumab.af.
14. actemra.tw.
15. il-6.tw.
16. anti-IL-6.tw.
17. anti-interluekin-6.tw.
18. interluekin-6.tw.
19. or/10-18
20. 9 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. drug therapy.fs.
26. randomly.ab.
27. trial.ab.
28. groups.ab.
29. or/21-28
30. (animals not (humans and animals)).sh.
31. 29 not 30
32. 20 and 31

EMBASE 2007 to 2009 Week 26

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (rheumat$ or reumat$ or revmarthrit$).tw.
4. (felty$ adj2 syndrome).tw.
5. (caplan$ adj2 syndrome).tw.
6. (sjogren$ adj2 syndrome).tw.
7. (sicca adj2 syndrome).tw.
8. still$ disease.tw.
9. bechterew$ disease.tw.
10. or/1-9
11. Atlizumab/
12. Interleukin 6 Receptor/
13. Interleukin 6/
14. Tocilizum$.tw.
15. atlizumab.tw.
16. actemra.tw.
17. il-6.tw.
18. anti-IL-6.tw.
19. anti-interluekin-6.tw.
20. interluekin-6.tw.
21. or/11-20
22. 10 and 21
23. random$.ti,ab.
24. factorial$.ti,ab.
25. (crossover$ or cross over$ or cross-over$).ti,ab.
26. placebo$.ti,ab.
27. (doubl$ adj blind$).ti,ab.
28. (singl$ adj blind$).ti,ab.
29. assign$.ti,ab.
30. allocat$.ti,ab.
31. volunteer$.ti,ab.
32. crossover procedure.sh.
33. double blind procedure.sh.
34. randomized controlled trial.sh.
35. single blind procedure.sh.
36. or/23-35
37. exp animal/ or nonhuman/ or exp animal experiment/
38. exp human/
39. 37 and 38
40. 37 not 39
41. 36 not 40
42. 22 and 41

The Cochrane Library Issue 2, 2009

#1 MeSH descriptor Arthritis, Rheumatoid explode all trees in MeSH products
#2 felty near/2 syndrome in All Fields in all products
#3 caplan near/2 syndrome in All Fields in all products
#4 sjogren* near/2 syndrome in All Fields in all products
#5 sicca near/2 syndrome in All Fields in all products
#6 still* next disease in All Fields in all products
#7 bechterew* next disease in All Fields in all products
#8 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab

#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Receptors, Interleukin-6 explode all trees
#11 MeSH descriptor Interleukin-6, this term only
#12 Tocilizum*:ti,ab
#13 altizumab:ti,ab
#14 actemra:ti,ab
#15 il-6:ti,ab
#16 anti-IL-6:ti,ab
#17 anti-interluekin-6:ti,ab
#18 interluekin-6:ti,ab
#19 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
#20 (#9 AND #19)

CINAHL

S33 S19 and S32 SearchS32 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31S31 TI Allocat* random* or AB Allocat* random*S30 (MH "Quantitative Studies")S29 (MH "Placebos")S28 TI Placebo* or AB Placebo* Search S27 TI Random* allocat* or AB Random* allocat*S26 (MH "Random Assignment") Search S25 TI Randomi?ed control* trial* or AB Randomi?ed control* trial*S24 AB singl* blind* or AB singl* mask* or AB doub* blind* or AB doubl* mask* or AB trebl* blind* or AB trebl* mask* or AB tripl* blind* or AB tripl* mask*S23 TI singl* blind* or TI singl* mask* or TI doub* blind* or TI doubl* mask* or TI trebl* blind* or TI trebl* mask* or TI tripl* blind* or TI tripl* mask*S22 TI clinical* trial* or AB clinical* trial*S21 PT clinical trial
S20 (MH "Clinical Trials+")
S19 S9 and S18
S18 (S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17)
S17 TI interluekin-6 or AB interluekin-6
S16 TI anti-interluekin-6 or AB anti-interluekin-6S15 TI anti-IL-6 or AB anti-IL-6S14 TI il-6 or AB il-6S13 TI actemra or AB actemraS12 TI altizumab or AB altizumab
S11 TI Tocilizum* or AB Tocilizum*S10 (MH "Interleukins+")
S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8S8 TI felty* N2 syndrome or AB felty* N2 syndrome or TI caplan* N2 syndrome or AB caplan* N2 syndrome or TI sjogren* N2 syndrome or AB sjogren* N2 syndrome or TI sicca N2 syndrome or AB sicca N2 syndrome or TI still* disease or AB still* disease
S7 TI revmarthrit* N3 arthrit* or AB revmarthrit *N3 arthrit* or TI revmarthrit* N3 artrit* or AB revmarthrit* N3 artrit* or TI revmarthrit* N3 diseas* or AB revmarthrit* N3 diseas* or TI revmarthrit* N3 condition* or AB revmarthrit* N3 condition* or TI revmarthrit* N3 nodule* or AB revmarthrit* N3 nodule*S6 TI reumat* N3 arthrit* or AB reumat *N3 arthrit* or TI reumat* N3 artrit* or AB reumat* N3 artrit* or TI reumat* N3 diseas* or AB reumat* N3 diseas* or TI reumat* N3 condition* or AB reumat* N3 condition* or TI reumat* N3 nodule* or AB reumat* N3 nodule*
S5 TI rheumatic N3 arthrit* or AB rheumatic N3 arthrit* or TI rheumatic N3 artrit* or AB rheumatic N3 artrit* or TI rheumatoid N3 diseas* or AB rheumatoid N3 diseas* or TI rheumatoid N3 condition* or AB rheumatoid N3 condition* or TI rheumatoid N3 nodule* or AB rheumatoid N3 nodule S4 TI revmatoid N3 arthrit* or AB revmatoid N3 arthrit* or TI revmatoid N3 artrit* or AB revmatoid N3 artrit* or TI revmatoid N3 diseas* or AB revmatoid N3 diseas* or TI revmatoid N3 condition* or AB revmatoid N3 condition* or TI revmatoid N3 nodule* or AB revmatoid N3 nodule* S3 TI reumatoid N3 arthrit* or AB reumatoid N3 arthrit* or TI reumatoid N3 artrit* or AB reumatoid N3 artrit* or TI reumatoid N3 diseas* or AB reumatoid N3 diseas* or TI reumatoid N3 condition* or AB reumatoid N3 condition* or TI reumatoid N3 nodule* or AB reumatoid N3 nodule*S2 TI rheumatoid N3 arthrit* or AB rheumatoid N3 arthrit* or TI rheumatoid N3 artrit* or AB rheumatoid N3 artrit* or TI rheumatoid N3 diseas* or AB rheumatoid N3 diseas* or TI rheumatoid N3 condition* or AB rheumatoid N3 condition* or TI rheumatoid N3 nodule* or AB rheumatoid N3 nodule*S1 (MH "Arthritis, Rheumatoid+")

Web of Knowledge
#3 random* or "control* trial*" or intervention* or experiment* or "time series" or "pre test" or pretest or "post test" or posttest or impact* or chang* or evaluat* or effect* or comparat*
#2 Tocilizum* or altizumab or actemra
#1 rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) and (arthrit* or artrit* or diseas* or condition* or nodule*))) OR Topic=((felty* or caplan* or sjogren* or sicca* or still*) and (disease or syndrome))

Dissertation Abstracts
Tocilizum* OR altizumab OR actemra in Citation and abstract

Current Controlled Trials
Tocilizum* OR altizumab OR actemra

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