

STUDY	Incomplete Outcome Data Judgement	Incomplete Outcome Data Reason	Selective Outcome Reporting Judgement	Selective Outcome Reporting Reason	Major Baseline Imbalance Judgement	Major Baseline Imbalance Reason	Serious AE Definitions Judgement	Serious AE Definitions Reason	Method of AE Monitoring Judgement	Method of AE Monitoring Reason
Abe 2006	Low Risk of Bias	page 38, right column:...The analysis set of demographics and efficacy was the full analysis set..... Five patients receiving the placebo discontinued treatment, including 3 due to lack of efficacy, one due to an adverse event, and one due to a protocol violation. Five patients receiving infliximab discontinued treatment due to adverse events.....	Low Risk of Bias	page 38 left column: The primary endpoint of the DBT was a response rate of a 20% improvement according to the ACR criteria (ACR20)18 at Week 14. Evaluations were made in terms of improvement of 20%, 50%, and 70% according to the ACR response (ACR20, ACR50 and ACR70) and individual measurements of the ACR core set at Weeks 0, 2, 6, 10, and 14 in the DBT	Low Risk of Bias	page 38, right column: Baseline demographics were comparable among the 3 groups, with the exception of body weight (Table 1).	Unclear	not explicitly described	Low Risk of Bias	In the DBT, patients were monitored for safety until just before the first infusion of the OLT.
Bozkurt 2001	Low Risk of Bias	page 1045, right column: Of the 31 patients who received etanercept, 27 completed 3 months of therapy (75% in the 5 mg/m2 group and 100% in the 12 mg/m2 group); all of the patients in the placebo group finished 3 months of blinded therapy.	Low Risk of Bias	page 1044: The primary objective was to evaluate the safety and tolerability of etanercept.	Low Risk of Bias	page 1045, left column: Table 1 shows the baseline characteristics of the study population. There was no significant difference in important factors	Unclear	no explicit category serious ae reported	Low Risk of Bias	page 1045, left column: Patients were evaluated for adverse events throughout the study. In addition to serially monitoring heart rate and blood pressure, we also assessed hemoglobin/hematocrit, white blood cell count, platelet count, serum electrolytes, and serum creatinine. Assessment for antibodies to etanercept were performed as described previously at baseline and at the end of 3 months of blinded therapy.
Chen 2009	Low Risk of Bias	page 313, left column: Forty-seven RA patients who were enrolled in the ITT population were randomized into treatment groups (35 in the adalimumab plus MTX group and 12 in the MTX alone group). Page 314: Table 2	Low Risk of Bias	page 312, right column: Patients were assessed for the primary efficacy endpoint (the ACR20 response at week 12 in the modified full analysis set, 19	Low Risk of Bias	page 313, right column: As illustrated in Table 1, demographics were comparable between the two treatment groups.	Unclear	use of term severe instead of serious	Low Risk of Bias	page 312, right column: Monitoring of vital signs, physical examinations, laboratory parameters (hematology, blood chemistry, CRP, routine urinalysis), and adverse events (AEs) was performed every month for safety evaluation.
Emery 2008a	Low Risk of Bias	page 376: figure 1	Low Risk of Bias	page 378 left column: At 52 weeks, the proportion of participants who achieved DAS28 remission ...	Low Risk of Bias	page 377: table 1	Unclear	not explicitly described	Unclear	active monitoring not explicitly stated
Genovese 2008	Low Risk of Bias	page 2970: figure 1	Low Risk of Bias	page 2970 left column: The primary end point was the proportion of patients who had achieved a response according to the ACR criteria for 20% improvement (ACR20) (22) at week 24. page 2971 right column	Low Risk of Bias	page 2970 right column: The 2 groups were well balanced with respect to demographics, baseline disease characteristics, and concomitant DMARD, glucocorticoid, and NSAID use at baseline (Table 1).	Unclear	not explicitly described	Low Risk of Bias	page 2970 left column: Safety was assessed by examining adverse events (AEs), serious AEs, infections, withdrawals due to AEs, deaths, and clinically significant changes in vital signs and laboratory test results.
Gordon 2006	Low Risk of Bias	page 601 left column: The majority of patients (95% [140 of 147]) completed the initial 12-week study with no differences observed in the percentage of completers across treatment groups: 90% (132 of 147) of patients completed 24 weeks, and 72% (106 of 147) of patients completed 60 weeks of treatment	Low Risk of Bias	page 600 right column: The primary efficacy analysis was the percentage of patients achieving at least a 75% improvement in PASI score (PASI 75) relative to baseline at week 12. Safety evaluations were conducted through patient histories and physical examinations including vital signs, laboratory evaluations, chest radiographs, and electrocardiograms.	Low Risk of Bias	page 601 right column: Patients were well balanced across treatment groups with respect to demographic characteristics and baseline disease activity (Table 1).	Unclear	not explicitly stated	Low Risk of Bias	page 600 right column: Safety evaluations were conducted through patient histories and physical examinations including vital signs, laboratory evaluations, chest radiographs, and electrocardiograms.
Hainsworth 2005	High Risk of Bias	page 1090 right column: Thirty-one of 44 patients in the maintenance rituximab group received at least one course of maintenance treatment. Page 1091 left column: Of the patients randomly assigned to rituximab retreatment at progression, 27 (59%) of 46 have received at least one retreatment course of rituximab	Unclear	page 1090 left column: Routine follow-up included repeat physical examination with tumor measurements, CBCs, and chemistry profile every 3 months, and repeat CT scans at least every 6 months.	Low Risk of Bias	page 1090 right column: Prognostic factors were relatively well balanced between the two treatment groups.	Unclear	not explicitly stated	Unclear	page 1090 left column: Routine follow-up included repeat physical examination with tumor measurements, CBCs, and chemistry profile every 3 months, and repeat CT scans at least every 6 months.
Hanauer 2006	Low Risk of Bias	page 324 right column: Data for all 299 randomized patients were included in the safety analysis.	Low Risk of Bias	page 327 figure 2. page 329 table 2	Low Risk of Bias	page 326 left column: The baseline characteristics of the patients who received placebo were similar to those who received adalimumab (Table 1).	Unclear	not explicitly stated	Low Risk of Bias	page 324 right column: At each visit, adverse events and concomitant medications were recorded and samples were collected for laboratory evaluations. Safety assessments included vital signs, physical examinations, hematologic analysis, serum biochemistry analysis, and urinalysis.
Hawker 2009	Low Risk of Bias	page 465 table 2	Low Risk of Bias	page 466 table 3 and page 468 table 4	Low Risk of Bias	page 462 right column: Baseline characteristics (Table 1) of 439 patients were balanced between treatment groups.	Unclear	not described	Low Risk of Bias	page 462 left column: An independent Data Monitoring Committee met formally every 3 months to review unblinded safety data, including MRI outcomes, clinical outcomes, and adverse events.
Jatoi 2007	High Risk of Bias	>20% dropped out prior to AE assessment	High Risk of Bias	no information on key outcomes	Unclear	ethnicity and other important characteristics	Unclear	not described	Low Risk of Bias	regular assessment by physician plus patient questionnaire
Miyasaka 2008	Low Risk of Bias	adequate analysis and FU	Low Risk of Bias	judgement call	Unclear	important baseline characteristics not reported (e.g. ethnicity)	Unclear	not described	Low Risk of Bias	regularly monitoring for AEs by lab assessments and physical examinations
Reich 2005	Low Risk of Bias	adequate analysis and FU	Low Risk of Bias	judgement call	Unclear	important baseline characteristics not reported (e.g. ethnicity)	Unclear	not described	Low Risk of Bias	regularly lab assessments
Zachariae 2008	Low Risk of Bias	adequate analysis and FU	Low Risk of Bias	judgement call	Unclear	some imbalance in gender	Unclear	not described	Low Risk of Bias	regularly lab assessments + physical examinations
Brandt 2003	Low Risk of Bias	An intent-to-treat-analysis was performed. Three patients were withdrawn shortly after randomization before receiving the study drugs. These three patients were excluded from further analysis. A fourth patient dropped out after 1 week of treatment due to lack of compliance.	Low Risk of Bias	as primary endpoint of the study an improve in disease activity was chosen (BASDAI). Secondary outcomes were improvements in numeric rating scales (spinal pain, BASFI, BASMI, SF-36, ASAS response criteria, CRP ESR, time to relapse)	Low Risk of Bias	treatment groups showed no significant differences in terms of sex distribution, disease duration, HLA-B 27 status, radiographic changes in the spine, clinical disease parameters	Unclear	not described	Unclear	not described

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Chaudari 2001	Low Risk of Bias	1/11 dropped out in each group	Low Risk of Bias	The Physician's global Assessment (PGA) at week 10 was the predefined primary efficacy endpoint. Secondary endpoint Psoriasis Area Severity Index, adverse events	Low Risk of Bias	The three treatment groups were similar with regard to sex, age range, baseline disease severity	Unclear	not described	Low Risk of Bias	Patients were monitored for the occurrence of all adverse events.
Emery 2008b	High Risk of Bias	flowchart: more than 20% withdrawn/rescue therapy in each arm, AEs: Events that occurred on escape therapy were excluded	Low Risk of Bias	primary endpoint: ACR 20 response at week 24, secondary: further efficacy measure. Safety outcomes included adverse events, infections, infusion reactions	Low Risk of Bias	three groups were reasonably well balanced for demographics and RA characteristics at baseline	Unclear	not described	Low Risk of Bias	Safety outcomes included adverse events, infections and infusion reactions
Fleischmann 2009	Low Risk of Bias	safety population: all randomized patients who received >= 1 dose of study drug; censored at the time of the first event for those with an event under consideration	Low Risk of Bias	Primary efficacy endpoint was ACR20 response at week 24, secondary endpoints included ACR50/70 response, ACR component scores, DAS ESR, patient-reported outcomes (HAQ-DI), HRQoL, SF-36, pain (VAS), mBPI, fatigue, safety	Low Risk of Bias	Patient baseline demographics and disease activity were similar between treatment arms; Females unequal distributed	Low Risk of Bias	per the Medical Dictionary for Regulatory Activities	Low Risk of Bias	Safety was assessed by recording all reported Aes at each visit
Forstpointner 2002	Low Risk of Bias	Interim report	Low Risk of Bias	endpoints: complete remission rate, event-free survival, progression-free survival, overall survival	Low Risk of Bias	reasonably well balanced	Low Risk of Bias	according to NCIC Common toxicity Criteria	Unclear	not described
Gorman 2002	Low Risk of Bias	ITT	Low Risk of Bias	primary endpoint: composite of improvements in measuring morning stiffness, spinal pain, functioning, disease activity and joint swelling. Secondary: physician's assessment of disease activity, spinal mobility, enthesitis, joint-tenderness, ESR, CRP	High Risk of Bias	There were no statistical significant differences between the study groups that may have indicated the presence of more severe disease in the etanercept group (SF-36, hb-level)	Low Risk of Bias	CTC	Low Risk of Bias	side effects were monitored at each clinic visit by means of open-ended questions
Inman 2008	Low Risk of Bias	ITT, safety analysis: all patients with at least one dose of Golimumab	Low Risk of Bias	primary endpoint was the proportion of patients with at least 20% improvement in the ASAS20 criteria at week 14, secondary endpoints: ASAS40% improvement, ASAS partial remission, ASAS5/6, BASDAI, back pain VAS, night pain VAS, patient's global assessment, CRP level, BASFI, BASMI, SF-36, JSEQ, golimumab concentration	Low Risk of Bias	Demographic and baseline disease characteristics were generally well balanced across treatment groups, except for disease duration, which was shorter in the golimumab group	Unclear	not described	Unclear	not described
Jarnerot 2005	High Risk of Bias	It was planned that the interim analysis would be performed and that the future of the study would be decided after 70 patients had been treated. Interim analysis after 45 patients due to slow element	Low Risk of Bias	primary endpoint: colectomy or death within 90 days after infusion. Secondary endpoints: clinical and endoscopic remission	High Risk of Bias	sex, smokers, earlier known of colitis ulcerosa, azathioprine at the time of inclusion were unequal distributed	Unclear	not described	Unclear	not described
Kay 2008	High Risk of Bias	Two interim analyses were conducted by the sponsor on data acquired through week 16 to aid the clinical development program, including the selection of dosages for the phase III studies	Low Risk of Bias	primary endpoint: ACR20% improvement at week 16; secondary endpoints included improvement from baseline at week 16 in the DAS28, ACR-N, ACR 20, ACR50 and ACR70 responses over time through week 52	High Risk of Bias	the population was somewhat heterogenous because of the small number of patients in each treatment group. Statistical tests were performed only for the combined golimumab group compared to placebo (no statistically significant differences).	Unclear	not described	Unclear	not described
Keystone 2004a	High Risk of Bias	Discontinuations occurred in 92 patients (22%) in the adalimumab group and 60 patients (30%) in the placebo group	Low Risk of Bias	primary endpoint: ACR20 response at week 20	Low Risk of Bias	there were no statistical significant differences in any demographic or baseline characteristic between the placebo group and the 2 adalimumab dosage groups. In these relatively small patient groups, there were some between-group differences in demographic characteristics, baseline medication, or baseline disease activity, but these did not reach statistical significance	Unclear	not described	Unclear	not described
Maini 1998	Low Risk of Bias	Safety was monitored until the end of the twenty-sixth week of the trial, whether or not the patient was continuing with trial medication.	Low Risk of Bias	primary efficacy endpoint: the total time in weeks that a patient exhibited a response to treatment	Low Risk of Bias		Unclear	not described	Low Risk of Bias	Safety was monitored until the end of the twenty-sixth week of the trial, whether or not the patient was continuing with trial medication.
Mease 2004	High Risk of Bias	69% of placebo patients and 92% of etanercept patients completed 24 weeks of therapy	Low Risk of Bias	primary endpoint: ACR20, other endpoints included: ACR 50 and ACR 70, PsARC, SF-36 and HAQ	Low Risk of Bias	The groups were well matched in terms of disease history, age and race. A slight predominance of women was observed in the placebo group (55%) and of men in the etanercept group (57%)	Low Risk of Bias	NCIN CTC	Unclear	not described
Mease 2005	Low Risk of Bias	approximately 92% from each group completed the 24-week study	Low Risk of Bias	Primary efficacy endpoint: ACR20 response at 12 weeks. Secondary endpoints were measures of joint disease, disability and quality of life as well as skin disease in those patients with psoriasis involving at least 3% of body surface area	Low Risk of Bias	the demographic characteristics and measures of disease severity in the patients at baseline were comparable between treatment groups	Unclear	not described	Unclear	not described
Present 1999	Low Risk of Bias	ITT	Low Risk of Bias	Primary efficacy endpoint was defined a priori as a reduction of 50 percent or more from baseline in the number of draining fistulas observed at two or more study visits, Secondary endpoints were complete response, the length of the beginning of a response, and the duration of the response	Low Risk of Bias	Demographic and clinical characteristics and rates of use of concomitant medications were similar in all treatment groups	Unclear	not described	Low Risk of Bias	patients were monitored for adverse events during each infusion and at each study visit.
Salles 2007	Low Risk of Bias	ITT	Low Risk of Bias	primary endpoint: EFS, secondary endpoints: toxicity, response rate and overall survival	Low Risk of Bias	no differences were observed in the distribution of these characteristics between the two treatment groups	Low Risk of Bias	toxicity was assessed using the NCIC Toxicity scale	Unclear	not described
Schiff 2008	Low Risk of Bias	ITT, more than 92% completed six months therapy	Low Risk of Bias	primary endpoint: reduction in disease activity, secondary endpoints included mean reduction in DAS28, HAQ-DI, mean changes in the physical and mental component summary scores, and eight subscales of the SF-36	Low Risk of Bias	Baseline demographics and clinical characteristics were similar between groups	Unclear	not described	Low Risk of Bias	safety was assessed at each visit
Weinblatt 2003	High Risk of Bias	ITT, 161 of 271 that entered the study completed 24 weeks	Low Risk of Bias	the primary efficacy endpoint was the ACR20 at 20 weeks, secondary efficacy endpoints included the ACR50 and the ACR70 response rates and improvements in ACR core set of disease activity measures, HAQ, SF-36, FACIT	Low Risk of Bias	There were no statistical significant differences in the demographic and baseline characteristics among the treatment groups	Low Risk of Bias	according to the Hoechst Adverse Reaction Terminology System	Low Risk of Bias	patients were monitored for adverse events during the entire study

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Wiedemann 2008	Low Risk of Bias	all patients were analysed in the safety population	Low Risk of Bias	primary endpoint: change in lean body mass, secondary endpoints: overall survival, progression-free survival, 6-minute walk distance, quality of life	Low Risk of Bias	patients were comparable in baseline clinical and demographic features, except that more men were in the placebo group than in the groups receiving infliximab	Unclear	not described	Unclear	not described
Cohen 2006	Unclear	54% of placebo patients completed study compared to 82% of tx group. Most placebo withdrawals were due to no response	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	Sociodemographics balanced at baseline	Low Risk of Bias	definition provided	Low Risk of Bias	actively monitor for AEs
Durez 2007	Low Risk of Bias	2 patients in MTx grp dropped out compared to 1 in the infliximab group and 1 in the IV MP group	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	baseline demographic, clinical, biologic, and radiographic characteristics did not differ between groups	Unclear	No definition provided	High Risk of Bias	spontaneous reporting of Aes
Gottlieb 2003	Low Risk of Bias	At 12 weeks (the time point for primary efficacy evaluation), 53 (93%) of the 57 etanercept-treated patients and 40 (73%) of the 55 placebo-treated patients were still receiving the study drug. At 24 weeks, 48 (84%) of the etanercept-treated patients and 12 (22%) of placebo patients remained in the study	Low Risk of Bias	All expected outcomes reported	Low Risk of Bias	Patients well matched in terms of demographics and disease activity at baseline	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Kavanaugh 2009	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	All expected outcomes reported	Low Risk of Bias	groups balanced at baseline	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Leonardi 2003	Unclear	similar proportions of patients completed treatment in each group - 27 patients withdrew due to Aes, 16 withdrew due to lack of efficacy, actual numbers per group were not reported	Low Risk of Bias	all expected outcomes were reported	Low Risk of Bias	The groups were balanced in terms of demographic characteristics, disease history, and the severity of disease at baseline	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Mease 2000	Low Risk of Bias	All patients in treatment group completed study - 4 patients in placebo group dropped out - 3 for lack of efficacy or refusal and 1 lost to follow-up	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	The groups were well balanced in all characteristics except that twice as many patients in the placebo group were receiving corticosteroids than in the etanercept group, and in the groups evaluable for psoriasis, the placebo group had lower baseline PASI scores.	Unclear	no definitions provided	Low Risk of Bias	actively monitor for Aes
Ortonne 2008	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	all expected outcomes were reported	Low Risk of Bias	Baseline demographic and disease characteristics were not significantly different between the continuous and paused treatment groups	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Zein 2005	Low Risk of Bias	3 patients withdrew - 1 from placebo 2 from tx	Low Risk of Bias	expected outcomes reported	Low Risk of Bias	No statistically significant difference existed between the two groups with respect to age, sex, ethnicity, body mass index, HCV genotype, histology activity index, or degree of fibrosis.	Unclear	definition provided	Low Risk of Bias	actively monitor for AEs
St Clair 2004	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	The characteristics of the 1,004 study patients with RA were similar among the 3 treatment groups	Low Risk of Bias	Two patients (0.5%) in each of the MTX-infliximab groups had infusion reactions classified as serious by the investigators according to the regulatory definition.	Low Risk of Bias	actively monitor for AEs
Smolen 2009	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	No difference in demographics. Across study sites, patients with similar disease activity were enrolled, irrespective of the number of patients enrolled by each site	Low Risk of Bias	definition provided	Low Risk of Bias	actively monitor for AEs
Sandborn 2007b	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	The baseline characteristics of the randomised patients who received placebo were similar to those who received adalimumab	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Sandborn 2007a	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Unclear	congestive heart disease not reported, nomenclature of "hypertensive heart disease" used in describing death of one patient in the certolizumab arm, nature of severe infections were not well characterized	Low Risk of Bias	The baseline characteristics were similar in the two groups	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Sandborn 2001	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	The baseline characteristics of the 2 groups of patients were similar	Low Risk of Bias	All adverse events were recorded and graded according to COSTART dictionary criteria	Low Risk of Bias	actively monitor for AEs
Rossmann 2006	Low Risk of Bias	3 drop outs - study is small	Unclear	Many of the classical AEs associated with TNFa antagonists were not addressed (either directly or indirectly)	Unclear	twice as many patients in infliximab group compared to placebo, placebo group was 83% male compared to 38.5 % in infliximab, clinical variables appear similar at baseline	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Kremer 2006	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Low Risk of Bias	all expected outcomes reported	Low Risk of Bias	Baseline demographic or clinical characteristics did not notably differ between treatment groups	Low Risk of Bias	we deemed an event as serious by standard regulatory definition	Low Risk of Bias	actively monitor for AEs
Rennard 2007	Low Risk of Bias	completion rate slightly <80 but reasons for discontinuation explained, appropriate outcomes were reported	High Risk of Bias	most expected outcomes were reported, AEs were described as including allergies but allergic reactions to biologic were not quantified, similarly with fungal infections; and "There was no difference in the total number of fungal, mycobacterial, or antibiotic-requiring infections, and no infection-related mortality was observed.	Low Risk of Bias	Overall, baseline demographics and disease characteristics were well balanced across the treatment arms	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs

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Pfreundschuh 2006	Low Risk of Bias	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	Unclear	adverse event analysis did not use ITT values. Rather, it excluded patients who did not receive the study treatment and one patient whose data was lost.	Low Risk of Bias	appears to be balanced by age and gender at entry (extractor judgment)	Low Risk of Bias	AEs graded according to US National Cancer Institute common toxicity criteria	Low Risk of Bias	actively monitor for AEs
Ribrag 2009	Unclear	not described	Low Risk of Bias	expected outcomes reported	Low Risk of Bias	sociodemographics appear balanced	Unclear	no definitions provided	Low Risk of Bias	actively monitor for AEs
Antoni 2005b	Low Risk of Bias	95% of the patients completed the study and follow-up	Unclear	1 major AE is lacking	Low Risk of Bias	The baseline characteristics for the 2 treatment groups were generally similar, with a few exceptions.	Unclear	not described	Unclear	not described
Aviles 2007a	Unclear	not described	Unclear	1 major AE and 3 minor AE are lacking	Low Risk of Bias	No statistical differences were observed between the two arms	Low Risk of Bias	Toxic effects were evaluated according to the criteria of the National Cancer Institute	Unclear	not described
Breedveld 2006	High Risk of Bias	Completed the 2-year treatment period: adalimumab 60.9% [167/274 patients] and MTX 65.8% [169/257 patients]	Unclear	1 major AE and 4 minor AE are lacking	Low Risk of Bias	Demographic and baseline clinical characteristics of the patients reflected a population with early RA and were comparable among the 2 treatment groups.	Low Risk of Bias	AEs that were recorded as 'serious' were those that met regulatory guidance or required prolonged hospitalization, were life-threatening or resulted in death, caused significant or permanent disability, or in the opinion of the investigator, were significant medical events.	Unclear	Safety assessments, including the monitoring of adverse events (AEs) and measurements of laboratory parameters, were carried out at regular intervals during the course of the study.
Davis 2003	Low Risk of Bias	91% (Bio) and 86% (placebo) completed 24 weeks of therapy	Unclear	>1 major AE not reported	Low Risk of Bias	The groups were well matched in most characteristics of demographics and disease history.	Low Risk of Bias	Adverse events and abnormal laboratory values were graded on a scale derived from the National Cancer Institute Common Toxicity Criteria (online at http://ctep.cancer.gov).	Low Risk of Bias	All patients used a diary to record the presence of any adverse events. Study staff reviewed the diary with the patient at each visit. For the safety analyses, the types and intensities of adverse events and infections reported during the study were recorded.
Eve 2009	Unclear	Data were available on a total of 139/156 (89%) patients. No reason for missing data of 17 lost to follow-up.	High Risk of Bias	4 major and 5 minor AE are not reported.	Low Risk of Bias	No major imbalance. Both treatment arms had a median age of 63.5 years with a male predominance. The majority of patients had advanced stage disease (III or IV) with just under half having B symptoms and/or an elevated lactate dehydrogenase	Low Risk of Bias	All toxicity was graded according to the National Cancer Institute toxicity criteria grading scale. Markers of both hematological and non-hematological toxicity were analysed with only those events of Grade 3 or 4 severity taken into consideration for the statistical analysis.	Unclear	not described
Genovese 2002a	High Risk of Bias	63% of the BIO group and 59% of the MTX group completed the study at 2 years	Unclear	2 major AE are lacking	Low Risk of Bias	The demographic characteristics of the patients who entered year 2 of the study were similar among groups, and the cohort continuing in the second year was similar to the entire population of the original study at baseline	Unclear	not described	Low Risk of Bias	During the second year of the study, patients were evaluated every 3 months for safety
Herold 2007	High Risk of Bias	the authors declared to report data only on follicular lymphoma (56% of the randomised population) but they did not present the number of randomised FL patients	High Risk of Bias	Most Major AE were not reported.	Low Risk of Bias	Baseline demographic, clinical, and pathologic characteristics of the FL population were well balanced across treatment groups with the exception of sex	Low Risk of Bias	Toxicity graded in accordance with the National Cancer Institute of Canada Common Toxicity Criteria grading system.	Low Risk of Bias	After completion of induction treatment, patients were observed every 8 weeks during the first year, at 3-month intervals during the second year, and then every 6 months from the third year onward.
Lin 2005					Low Risk of Bias	No major imbalance				
Naveau 2004	Low Risk of Bias	Only 1/18 patients in BIO group and 2/18 patients in the placebo group were lost.	Unclear	1 major and 3 minor AE are lacking	Low Risk of Bias	Imbalance for sex	Unclear	not described	Low Risk of Bias	Patients were examined at least once weekly until treatment completion to ensure that no complications had arisen. Patients were assessed at 2, 3, 6, 9, and 12 months after completion of treatment.
Papp 2005	Low Risk of Bias	More than 80% completed the randomised study at 12 weeks	High Risk of Bias	The majority of AE were not reported or impossible to assign to the comparison groups	Low Risk of Bias	The groups were well matched across treatment groups for demography and disease history	Low Risk of Bias	Adverse events and abnormalities in laboratory values were graded on a scale derived from the Common Toxicity Criteria of the National Cancer Institute.	Unclear	Safety was assessed throughout the study by summarizing reports of adverse events, infections and injection site reactions (ISRs); abnormalities in laboratory variables; and antibody formation to etanercept.
Salvarani 2007	Low Risk of Bias	91% completed the study through week 52	Unclear	3 major AE not reported	Low Risk of Bias	Baseline characteristics for the 2 groups were similar	Unclear	Patients reported adverse events, which we defined as a new diagnosis or incidence of any condition during the scheduled visits or at any time throughout the study.	Low Risk of Bias	At each visit, patients were asked which adverse events (from a predefined list of possible adverse events that was read to them) they had experienced. In addition, they were instructed during the first visit to voluntarily report to the investigator any adverse events that might occur during the study.
Spahr 2002	Low Risk of Bias	All patients completed the study	Unclear	3 major AE not reported	High Risk of Bias	there was imbalance for gender and age although tissue pathology was similar	Unclear	not described	Unclear	The patients' clinical evolution was recorded during a 3-month period.

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Weinblatt 2006a	Low Risk of Bias	More than 80% completed the study	Unclear	1 major and 2 minor AE are lacking	Low Risk of Bias	The treatment groups were similar with respect to demographic characteristics and most baseline disease characteristics, with the exception of the C-reactive protein level, which was slightly higher in the subgroup receiving nonbiologic background therapy	Low Risk of Bias	An AE was defined as any new or worsening illness, sign, symptom, or clinically significant laboratory test abnormality noted by the investigator or patient during the course of the study, regardless of causality. Intensity was rated by the investigator on a scale of 1 (mild) to 4 (very severe). An SAE was defined as an AE that met any of the following criteria: was fatal, was life-threatening, resulted in hospitalization, resulted in persistent or significant disability or incapacity, was a malignancy, was a congenital anomaly or birth defect, resulted in an overdose or drug dependency, or was deemed an important medical event, as determined by the investigator. The severity of AEs (including infections) was assessed by the investigator.	Unclear	All patients who received at least 1 dose of study medication were evaluated for the occurrence of adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, death, clinically significant changes in vital signs, physical examination abnormalities, and clinical laboratory test abnormalities.
Weisman 2007	Unclear	not described	Unclear	2 major and 5 minor AE are lacking	Low Risk of Bias	At baseline, the treatment groups were well balanced demographically, and the distribution of specific comorbidities was generally similar across groups	Low Risk of Bias	Serious adverse events (e.g. events that necessitate hospitalization, are life threatening, or result in significant disability or death)	Unclear	Evaluations were performed at baseline, weeks 8 and 16, and 30 days post-therapy.
Weisman 2003	Low Risk of Bias	All patients were included in analysis	High Risk of Bias	Most Major AE were not reported.	Low Risk of Bias	Although there was some variability in characteristics between treatment groups, the differences were not greater than the SDS	Unclear	not described	Low Risk of Bias	Assessment of the safety profile was based on adverse events reported by patients, as well as on the findings of physical examinations and clinical laboratory evaluations. During the double-blind phase, physical examinations and clinical laboratory evaluations were performed at baseline, 24 hours after administration of study drug, and on days 8, 15, 22, and 29.
Bathon 2000	Low Risk of Bias	>80% completion	High Risk of Bias	side effects occurring in >10%	Low Risk of Bias	refer to table 1	Low Risk of Bias	graded by NCI criteria	Unclear	not described
Cohen 2005	Low Risk of Bias	>80% completion	Unclear	no AE's reported	Unclear	sex, disease duration, and VAS characteristics aren't that similar	Unclear	not described	Unclear	not described
Edwards 2004	Low Risk of Bias	all outcome data present, >80% completion	High Risk of Bias	important side effects missing, some side effects shown only occurred in at least 10% patients	Low Risk of Bias	refer to table 1	Low Risk of Bias	A serious AE was defined as any event that was fatal, was life-threatening, required hospitalization, resulted in persistent or substantial disability or incapacity or in a congenital anomaly or birth defect, or was medical significant or required intervention to prevent any of the outcomes mentioned	Low Risk of Bias	adverse events were recorded at each visit
Emery 2006	Low Risk of Bias	all outcome data present, >80% completion	High Risk of Bias	important side effects missing, only report those SE greater than or equal to 5%	Low Risk of Bias	refer to table 2	Low Risk of Bias	graded according to NCI	Unclear	not described
Emery 2009	Low Risk of Bias	>80% completion, all primary outcomes reported	Unclear	not described	Low Risk of Bias	refer to table 1	Unclear	not described	Low Risk of Bias	safety assessments included adverse events
Gavalas 2007	Unclear	not described	Unclear	missing important side effects	Unclear	age, gender, disease duration quite varied	Low Risk of Bias	serious AEs were defined as clinical symptoms that required additional medical treatment or hospitalization	Low Risk of Bias	adverse events were recorded at follow-up visits
Ghielmini 2005	Unclear	not described	High Risk of Bias	report only serious adverse events considered possibly or probably related to treatment	Unclear	not described	Low Risk of Bias	requiring hospitalization	Unclear	not described
Hanauer 2002	Unclear	not described	Unclear	not described	Unclear	not described	Unclear	not described	Low Risk of Bias	adverse events were prospectively collected by direct questioning of participants
Hidemann 2005	Unclear	not described	Unclear	important side effects missing	Low Risk of Bias	refer to table 1	Unclear	not described	Unclear	not described
Keystone 2008	Low Risk of Bias	all primary outcomes, >80% completion	Low Risk of Bias	important side effects present	Low Risk of Bias	refer to table 1	Unclear	not described	Low Risk of Bias	safety evaluations were performed at weeks 1 and 2, then every 2 weeks until week 16, and then every 4 weeks thereafter until week 52 or at time of withdrawal
Klareskog 2004	Low Risk of Bias	>80% completion, reasons for missing outcome data balanced across groups	Low Risk of Bias	important side effects reported	Low Risk of Bias	refer to table 1	Low Risk of Bias	NCI	Low Risk of Bias	at patient visits throughout the study, we gathered reports of adverse events
Marcus 2005	Unclear	not described	Unclear	some expected side effects missing	Low Risk of Bias	refer to table 1	Low Risk of Bias	reported according to NCI common toxicity criteria	Unclear	not described

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van de Putte 2003	Low Risk of Bias	[87% bio completion rate] Efficacy analyses were performed for the intention to treat (ITT). All patients randomly allocated to receive adalimumab and who received at least one dose of adalimumab were included in the safety analyses.	Unclear	A 5 year old man taking adalimumab 80 mg died of a myocardial infarction on day 86 of the study... [no report on TB although a study of 2003]	Low Risk of Bias	The demographic and baseline characteristics of the study population (table 1) were similar for all treatment groups.	Low Risk of Bias	Additionally, AEs necessitating or prolonging hospitalisation, placing the patient at risk of death, or resulting in death, permanent or significant disability, congenital anomaly/birth defect, or other medically important conditions were categorised as serious AEs.	Low Risk of Bias	A complete physical examination was performed at study entry (screening), baseline, every two weeks, and, for those patients who withdrew, up to six months of follow up after the last study dose... Data on adverse events (AEs), such as type, time of occurrence, time to resolution, severity, and causal relationship to treatment, were collected at the baseline visit and at each subsequent study visit.
Sands 2001	Unclear	A formal statistical analysis of the results was not performed because of the small number of patients participating in the study. Descriptive statistics are presented where applicable... all patients received the entire infusion of study medication... [no deaths occurred during the study]	Low Risk of Bias	All patients reported at least one adverse experience during the study. [several safety outcomes not reported, but study from 2001]	Unclear	The demographic and baseline characteristics of the patients were reasonably balanced across the four groups, with the exception of slightly higher modified Truelove and Witts scores in the placebo- treated patients	Unclear	not described	Low Risk of Bias	All patients considered to be treatment failures continued to be monitored for safety. Safety evaluations during the study period included measurements of vital signs, hematology and clinical laboratory measurements, and occurrence of adverse experiences.
Rutgeerts 1999	Low Risk of Bias	patients who discontinued regularly scheduled follow-up or had a Crohn's disease-related surgical procedure or medication change not permitted by protocol had their measurements from the last observation carried forward... Of the 73 patients enrolled in the study, 67% received all 4 scheduled infusions of infliximab (73%) or placebo (61%)... All 73 patients enrolled were evaluated for efficacy, safety, and immunogenicity.	Low Risk of Bias	[key outcomes missing - tb, chf - preluded by year of study, 1999]	Unclear	patient demographic characteristics were well balanced across treatment groups with the exception of gender distribution, with more women randomly assigned to infliximab retreatment and more men to placebo retreatment (P 5 0.053) ... Baseline clinical characteristics were well balanced across treatment groups with the exception of baseline (week 0) serum CRP concentration	Unclear	not described	Low Risk of Bias	Patients were evaluated for efficacy and safety at 4-week intervals through week 48. Safety evaluations over the 36-week retreatment study period (weeks 12-48) were based on changes in clinical laboratory results, vital signs, physical examinations, and the incidence of adverse events, deaths, and premature discontinuations.
Rouhani 2005	High Risk of Bias	This trial was designed prospectively to enroll participants until both the TNFR:Fc and placebo groups had 13 completers. [no data provided for why the others discontinued] ... Eighteen of the 21 participants returned 1-month following the completion of the study and reported no interval change in asthma symptoms... our trial, which was suspended following a serious adverse event of transient hemiplegia.	Low Risk of Bias	Table 1 shows AE and notes SAE	Low Risk of Bias	There were no statistically significant differences in baseline characteristics between the TNFR:Fc and placebo groups	Unclear	not described	Unclear	not described
Menter 2007	Low Risk of Bias	Data from all randomized patients were analyzed according to assigned treatment group. [93% and 95% bio completion rates]	Low Risk of Bias	Through week 14, adverse events were more frequent in both infliximab induction groups than in the placebo group; however, the types of adverse events were similar. [most safety outcomes reported]	Low Risk of Bias	The demographic characteristics of the induction treatment groups were similar (Table I), and the mean percentage of involved BSA, types of prior therapies used, and mean baseline PASI and DLQI scores were comparable.	Unclear	not described	Low Risk of Bias	Infliximab safety and tolerability were assessed by monitoring adverse events, vital signs, and laboratory parameters through week 50.
Calin 2004	Low Risk of Bias	Intention to treat. Only 2 drop outs	High Risk of Bias	not all pre-specified outcomes reported; adverse events occurring in 5% or more of pts reported	Low Risk of Bias	Disease duration in Bio group 15 vs 9.7 years.	Unclear	No definition given	Low Risk of Bias	efficacy and safety evaluations were made at weeks 2,4,8,12
Buske 2009	Low Risk of Bias	all randomised analysed;	Unclear	All prespecified outcomes reported [some expected side effects not reported]	Low Risk of Bias	More males in non-bio group	Low Risk of Bias	WHO toxicity criteria	Unclear	WHO criteria
Antoni 2005a	Low Risk of Bias	<15% dropout in all arms. Last observation carried forward	Low Risk of Bias	None evident	Low Risk of Bias	generally well balanced	Unclear	No definitions given	Low Risk of Bias	Active assessment
Cohen 2004	Low Risk of Bias	Intention to treat.	Unclear	some safety outcomes not reported	Low Risk of Bias	Well balanced	Low Risk of Bias	Clear definitions given	Low Risk of Bias	Active assessment
Colombel 2007	High Risk of Bias	All patients accounted for in analysis [less than 80% bio completion]	Low Risk of Bias	None evident	Low Risk of Bias	Responders and non-responders to open label run in well balanced	Unclear	No definitions given	Low Risk of Bias	Active assessment
Combe 2006	Low Risk of Bias	LOCF for all randomised patients with exposure to drug	High Risk of Bias	events occurring in >5% pts reported	High Risk of Bias	Significantly more patients using steroids in the etanercept group	Low Risk of Bias	Some definition but not standardised... considered serious (requiring hospitalisation or treatment with parenteral antimicrobial agents)	Low Risk of Bias	active... Safety assessments were based on reports of adverse events and results of routine physical examinations and laboratory determinations
Genovesse 2005	Low Risk of Bias	All patients included if received drug. LOCF for dropouts. 20% dropout rate	Low Risk of Bias	Outcomes all reported	Low Risk of Bias	No differences	Unclear	No definitions	Low Risk of Bias	Adverse events sought and recorded
Marzo-Ortega 2005	Low Risk of Bias	LOCF and intention to treat	Unclear	not described	Low Risk of Bias	No differences	Unclear	No definitions	Unclear	Passive
Forstpointner 2004	Low Risk of Bias	86% bio completion rate	Unclear	imp side effects missing	Low Risk of Bias	refer to table 1	Low Risk of Bias	The frequency and severity of side effects were recorded according to the National Cancer Institute of Canada (NCIC) Common Toxicity Criteria (CTC).	Unclear	not described
Feugier 2005	Low Risk of Bias	Intention to treat for safety	Unclear	None evident	Low Risk of Bias	No difference	Unclear	No definitions	Unclear	not described
Foster 2003	Low Risk of Bias	Intention to treat	Unclear	important side effects missing	Low Risk of Bias	No difference	Unclear	No definitions	Low Risk of Bias	Active
Keystone 2009	Unclear	May be in online material	Low Risk of Bias	None evident	Low Risk of Bias	No difference	Unclear	No definitions	Unclear	no monitoring mentioned but Aes reported
Sandborn 2007	Low Risk of Bias	Intention to treat - all analysed	Low Risk of Bias	None evident	Low Risk of Bias	No differences	Low Risk of Bias	Standard regulatory definitions	Low Risk of Bias	Active
Smolen 2008	Low Risk of Bias	LOCF for all randomised patients with exposure to drug	Unclear	not described	Low Risk of Bias	No differences	Unclear	no definitions	Unclear	looks active as Aes well reported

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Torre-Amione 2007	Low Risk of Bias	Survival and adverse event analyses were done according to intent to treat; however, primary outcome analyses included only patients for whom data were available... [80% bio completion rate]	Unclear	not very detailed	Unclear	Patients were comparable with regards to baseline demographics... Significant difference in ages at baseline with younger treatment group	Unclear	not described	Unclear	not described
Tyden 2009	Unclear	Incidence of malignancies and all AEs missing	Unclear	not described	Low Risk of Bias	There was no significant difference, in gender, age, body weight, or body surface area. There were somewhat more living-donor transplantations in the placebo group, 25 of 68, vs. 19 of 68 in the rituximab group. On the other hand, there were more primary transplants in the rituximab group than in the placebo group, 68 vs. 62. There was no difference in the degree of immunization, mean panel reactive antibody being less than 5% in both groups.	Unclear	not described	Unclear	not described
van der Bijl 2009	Low Risk of Bias	[kaplan-meier of efficacy performed as intent-to-treat] ... completion rate implied as full	Unclear	not described	Low Risk of Bias	No significant differences for all parameters	Unclear	not described	Unclear	The occurrence of side effects was recorded during 6 months of follow-up.
van der Heijde 2006	Low Risk of Bias	Safety and efficacy analyses were performed on the intention-to-treat population, which was defined as all randomized patients who received at least 1 dose of the study medication. [94% completion in bio group]	Low Risk of Bias	cases of tuberculosis/granulomatous infections, demyelination, drug-induced lupus, congestive heart failure, and malignancies, and no deaths occurred during the 24 week period of the study.	Low Risk of Bias	Baseline demographic and clinical characteristics were similar across both treatment groups, except for history of psoriasis (Table 1). However, this difference was not considered clinically significant.	Unclear	not described	Low Risk of Bias	Treatment efficacy and safety were assessed at scheduled visits at weeks 2, 4, 8, 12, 16, 20, and 24. Adverse events and vital signs were assessed at every visit. Laboratory measurements were assessed at weeks 4, 12, 16, and 24.
Wegener's 2005	High Risk of Bias	Primary analyses were performed on an intention-to-treat basis. [61% bio completion rate]	Unclear	Only 38 patients in the etanercept group (42.7 percent) and 39 patients in the control group (42.9 percent) had no disease flares during the trial. During the study, 56.2 percent of patients in the etanercept group and 57.1 percent of those in the control group had at least one severe or life-threatening adverse event or died (P=0.90). Solid cancers developed in six patients in the etanercept group, as compared with none in the control group (P=0.01).	Low Risk of Bias	Fewer patients in the etanercept group than in the control group had newly diagnosed Wegener's granulomatosis at enrollment (34.8 percent vs. 53.9 percent, P=0.01), but the rate of previous exposures to cyclophosphamide, methotrexate, and azathioprine did not differ significantly between groups (data not shown). [similar ages%/female/ethnicity between groups shown in baseline characteristics table]	Low Risk of Bias	Adverse events, defined as any untoward medical occurrences in patients who received etanercept, regardless of their presumed relationships to treatment, were graded according to the National Cancer Institute Toxicity Grading Scale.	Unclear	Secondary outcome measures included...adverse events related to Wegener's granulomatosis or its treatment
Wenzel 2009	High Risk of Bias	The primary efficacy analyses used the intention-to-treat population; [42% bio completion rate]	Low Risk of Bias	SAEs, SAEs of an infectious nature, tuberculosis (class 3), death, malignancies were reported	Low Risk of Bias	Baseline demographics, disease characteristics, and concomitant medications were similar across all groups	Unclear	not described	Low Risk of Bias	Safety was assessed during each study visit and by monitoring adverse events (AEs) and serious adverse events (SAEs). Routine laboratory tests were assessed at baseline and Weeks 12, 24, 36, and 52. An independent Safety Monitoring Committee periodically reviewed all data and made recommendations to the Steering Committee regarding study continuation.
Barkham 2009	Low Risk of Bias	One patient (in the placebo group) withdrew consent at 12 weeks and discontinued participation in the study. This patient was included in the analysis of efficacy, because it was performed on an intent-to-treat basis. The remaining 39 patients completed the study	High Risk of Bias	[no total AEs, no TB reports, etc]	Low Risk of Bias	The randomized treatment groups were similar with regard to baseline demographic and disease characteristics	Unclear	No definition provided	Low Risk of Bias	Safety was assessed by monitoring patients for the occurrence of adverse events and by collecting samples for clinical laboratory testing at each visit
Coiffier 2002	Low Risk of Bias	The eight scheduled courses of chemotherapy were given to 72 percent of patients treated with CHOP and 80 percent of patients treated with CHOP plus rituximab.	Unclear	An adverse event was defined as any adverse change from the patient's base-line condition, whether it was considered related to treatment or not [no report of withdrawals due to AE, cancers, TB... etc]	Low Risk of Bias	There was no significant difference between the two groups in any clinical or pathological characteristic	Low Risk of Bias	Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system.	Low Risk of Bias	All adverse events reported by the patient or observed by the investigator were collected from the case-report form in predefined categories
den Broeder 2002	Low Risk of Bias	All randomized patients completed the double blind study except for one patient in the 0.5 mg/kg group, who received the study drug but withdrew after 25 days because of a serious adverse event (necrotizing pancreatitis); analyses through Day 29 were based on the intent-to-treat population within this period	Unclear	Safety and tolerability were evaluated based on reported adverse events, standard hematology and biochemistry measures and urinalysis, vital signs, and electrocardiogram (ECG); All patients in both adalimumab and placebo treated groups experienced at least one adverse event. [no report on TB, cancers, deaths, infections, etc]	Low Risk of Bias	No significant differences among study groups were detected in pretreatment characteristics or baseline disease activity	Unclear	not described	Low Risk of Bias	Safety and tolerability were evaluated based on reported adverse events
Genovese 2007	Low Risk of Bias	For efficacy and safety analyses, the intention-to-treat (ITT) population was defined as all patients who received at least one dose of study medication. [98% bio completion rate]	Low Risk of Bias	During the first 12 weeks, there were no cases of tuberculosis, granulomatous infection, demyelination, drug induced lupus, congestive heart failure, or malignancy and there were no deaths.	Low Risk of Bias	Overall, the baseline demographic data, medication usage, and disease severity characteristics were similar between treatment groups	Unclear	not described	Low Risk of Bias	The safety of adalimumab was assessed by measuring vital signs at every study visit, performing routine hematologic and clinical chemistry blood tests and urinalyses throughout the study, and recording adverse events (AE) throughout the study

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Kremer 2005	High Risk of Bias	All statistical analyses were carried out on the intent-to-treat (ITT) population, defined as all patients who received at least 1 treatment infusion; patients who discontinued for other reasons (than worsening RA) had their last observations carried forward. A total of 90 patients (78.3%) in the 10 mg/kg abatacept group, 74 (70.5%) in the 2 mg/kg abatacept group, and 71 (59.7%) in the placebo group completed 360 days of therapy	Low Risk of Bias	No abatacept-related deaths, cancers, opportunistic infections, or atypical presentations of infections were observed during this 12-month trial	Low Risk of Bias	All patients had comparable demographic and disease characteristics (duration of RA, number of tender joints, number of swollen joints, pain, and physical function) (Table 1). The use of MTX, oral corticosteroids, and other DMARDs prior to the study was similar among the groups (Table 1)	Low Risk of Bias	A serious AE was defined as an AE that was fatal or life threatening, resulted in or prolonged hospitalization, resulted in persistent or significant disability or incapacity, resulted in an overdose, resulted in the development of drug dependency or drug abuse, or was an important medical event. Serious AEs could also include cancer or congenital anomalies/birth defects. Patients were monitored for acute hypersensitivity reactions both during and following the administration of treatment	Low Risk of Bias	All patients were monitored for AEs, serious AEs, clinical laboratory test result abnormalities, and significant changes in vital signs.
Lan 2004	Low Risk of Bias	The efficacy analysis was performed in the intent-to-treat (ITT) population, which was defined as all patients with baseline data and at least 1 post-treatment evaluation. The last observation carried forward (LOCF) method was used to substitute for missing data; All 58 of these patients were included in the ITT population	High Risk of Bias	Adverse events observed in at least 5% of patients (listed) [no report of TB, cancer, CHF, death, etc]	Low Risk of Bias	There were no significant differences between the 2 groups in age, gender, and weight. The mean age of patients was 47.55 years in the etanercept plus MTX group and 50.79 years in the MTX alone group. There was a predominance of female patients in both groups (83% in etanercept plus MTX and 90% in MTX alone) [p = 0.446].	Unclear	AEs were described by using the Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary	Low Risk of Bias	Efficacy and safety evaluations were performed at monthly intervals
Maini 1999	Low Risk of Bias	An intention-to-treat analysis was done for the primary efficacy endpoint. Analyses of safety endpoints were undertaken with patients grouped as treated; three patients were reclassified from their randomised treatment groups in the safety analyses as described below.	Low Risk of Bias	No difference in the number of serious adverse events was noted among infliximab and placebo treated patients. During the 30 week trial there was no increase in serious infections requiring hospital treatment, but infections were more common in the 10 mg/kg regimens of infliximab than in the other treatment groups. In the continuing second 6 months of the trial one patient has developed tuberculosis and one coccidiomycosis (both on infliximab).	Low Risk of Bias	The baseline characteristics of the five treatment groups were well matched	Low Risk of Bias	The number of serious adverse events (requiring hospitalisation or judged life threatening)	Unclear	not described
Maini 2006	Low Risk of Bias	using an intent-to-treat full-analysis set. All patients who were allocated to receive study medication, had received at least 1 dose, and had postrandomization efficacy data available were included in the full-analysis set. All patients who withdrew because of lack of efficacy before the week 16 assessment were included in the analysis as nonresponders. For patients who withdrew because of other reasons, the last recorded assessment of the ACR20 response was carried forward	Low Risk of Bias	No cases of reactivation of tuberculosis were seen, and no opportunistic infections were observed in this study.	Low Risk of Bias	The baseline demographics of the treatment groups were similar, and no statistically significant differences were observed	Unclear	not described	Low Risk of Bias	Safety assessments included physical examinations, pre- and postdose electrocardiograms, and laboratory analyses of hematology, serum biochemistry, coagulation, immunologic parameters, and urine. Adverse events were recorded throughout the study.
Mariette 2004	Low Risk of Bias	Data on efficacy were analyzed for an intent-to-treat population, defined as all patients who underwent randomization and received at least one dose of the study medication. Missing values were imputed for the analysis with the use of a last observation carried forward method. [89% completion rate in bio group]	High Risk of Bias	[article only reports on SAEs]	Low Risk of Bias	The baseline data did not differ between the infliximab and placebo groups	Unclear	not described	Low Risk of Bias	Safety evaluations, which included all reports of adverse events, were conducted throughout the study.
Moreland 1999	High Risk of Bias	Patients who withdrew for any reason were counted as non-responders subsequent to withdrawal. The last available observation was used for dropouts. An intention-to-treat analysis was performed on the 234 patients who were randomly assigned and received the study drug. Significantly more etanercept recipients than placebo recipients completed the full 6 months of therapy: 76% in the 25-mg group and 68% in the 10-mg group compared with 33% in the placebo group	High Risk of Bias	[only reported for AEs that occurred in >10% of patients in any treatment group; no report on TB, CHF, total AEs, etc]	Low Risk of Bias	Aside from differences in concurrent medications (more patients in the 25-mg group were receiving corticosteroids and more placebo recipients were receiving NSAIDs), no baseline imbalances were detected.	Unclear	not described	Unclear	not described

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Saurat 2008	Unclear	All efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomized patients. Nonresponder imputation was used for the primary efficacy analysis.	Low Risk of Bias	There were no reports of tuberculosis, and no deaths occurred during the study.	Low Risk of Bias	Treatment groups were well-balanced with respect to baseline demographics, clinical characteristics and disease severity	Unclear	not described	Low Risk of Bias	Safety was assessed at all visits through week 16. Safety assessments, including adverse events, standard laboratory tests and vital signs, were assessed throughout the study and spanned a period through 70 days after last treatment.
Smolen 2009	High Risk of Bias	Efficacy analyses were conducted on the intention-to-treat (ITT) population (all randomised patients)... withdrew for any reason were considered non-responders from that time point onward. Safety analyses were conducted on the safety population (all patients who received treatment). 17 (13.4%) placebo patients completed the study versus 174 (70.7%) and 181 (73.6%) in the certolizumab pegol 200 mg and 400 mg groups, respectively	Low Risk of Bias	Important safety outcomes addressed	Low Risk of Bias	Patient demographics and baseline characteristics were similar in the three treatment groups and indicated high baseline disease activity	Unclear	not described	Low Risk of Bias	Safety was assessed at all visits, from screening through followup visits 12 weeks after the last dose for patients who did not enter the open-label extension phase.
van de Putte 2004	High Risk of Bias	Patients who dropped out were followed up at 1, 2, 3, and 6 months after treatment. An intention to treat analysis was performed that included patients who were randomised and who received at least one injection of the randomised study drug. Patients not completing the trial (that is, who were withdrawn or required rescue) despite fulfilling ACR criteria were considered nonresponders upon withdrawing or entering rescue. Withdrawals occurred in 118/434 (27.2%) adalimumab treated patients and 62/110 (56.4%) placebo treated patients.	Low Risk of Bias	There was no statistically significant difference between adalimumab and placebo treated patients in the rates of serious infection (2.3% v 0%, respectively), and no cases of primary or reactivation tuberculosis were seen during the study among adalimumab treated patients.	Low Risk of Bias	There were no statistically significant differences in the demographic characteristics and baseline disease activity between the treatment groups	Unclear	not described	Low Risk of Bias	Safety assessments were conducted at screening, baseline, and every study and follow up assessment.
van der Heijde 2005	Low Risk of Bias	All patients were analyzed for efficacy according to their randomly assigned treatment group, regardless of the actual treatment they received. All patients who received at least 1 study infusion were analyzed for safety according to the actual treatment they received. [199/201 bio patients and 75/78 placebo patients completed the trial]	Low Risk of Bias	No deaths, malignancies, or tuberculosis events were reported in this trial.	Low Risk of Bias	The treatment groups were well matched with regard to demographics and baseline clinical characteristics; however, there was a higher percentage of men in the placebo group (87.2%) compared with that in the infliximab group (78.1%).	Unclear	not described	Low Risk of Bias	Safety assessments included adverse events, infections, infusion reactions, premature discontinuation, and laboratory tests
Bliddal 2006	Low Risk of Bias	All data were analysed by intention to treat	Low Risk of Bias	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified	Unclear	No baseline measures reported	Unclear	No definition stated	Low Risk of Bias	After the injection of the trial substance, the patients were seen after weeks 1, 4, 8, 12, and 26. Patients were questioned about adverse events at all visits
Chevalier 2009	Low Risk of Bias	No missing outcome data	Low Risk of Bias	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified	Low Risk of Bias	No significant baseline imbalance observed	Unclear	not sufficient evidence to make judgement	Unclear	not sufficient information to make judgement
Coiffier 1998	Low Risk of Bias	2 dropped out; 1 per arm	Low Risk of Bias	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified	Low Risk of Bias	No significant baseline imbalance observed	Low Risk of Bias	Adverse events were graded according to the World Health Organization score	Low Risk of Bias	Safety assessments were performed for all patients for a minimum of 8 weeks
Combe 2009	Unclear	can't agree	Low Risk of Bias	Prespecified outcomes in methods reported in results	Low Risk of Bias	No significant baseline imbalance observed	Low Risk of Bias	An event was considered to be a treatment-emergent adverse event (TEAE) if it occurred during the study or if the severity or frequency of a preexisting event increased during the study. A serious adverse event (SAE) included any event resulting in death, hospitalisation or cancer. An infection was a serious infection if reported as an SAE	Low Risk of Bias	patients routinely questioned on AE
Ghielmini 2004	Low Risk of Bias	Number of patients in both group similar at the end of study period	Low Risk of Bias	Outcome prespecified and reported in results	Unclear	Not sufficient information to make judgement	Low Risk of Bias	The evaluation of toxicity was conducted according to the World Health Organization toxicity grading.	Unclear	not sufficient information to make judgement
Kavanaugh 2000	Low Risk of Bias	No dropout or loss to follow-up more than 90% of participants retained in trial	Low Risk of Bias	Outcome prespecified and reported in results	Low Risk of Bias	patient characteristics similar at baseline	Unclear	not sufficient evidence to make judgement	Low Risk of Bias	safety was evaluated at time intervals
Keystone 2004b	Low Risk of Bias		High Risk of Bias	AE reported in greater than 5% of patients	Low Risk of Bias	no major baseline imbalances observed	Unclear	not sufficient evidence to make judgement	Low Risk of Bias	grades using the National Cancer Institute
Kim 2007	High Risk of Bias	above 20% drop out or non responders	High Risk of Bias	AE reported in greater than 5% of patients	Low Risk of Bias	no major baseline imbalances observed	Low Risk of Bias	No definition stated	Low Risk of Bias	AE routinely followed up to 70 days in those loss to follow-up

STUDY	Incomplete Outcome Data Judgement	Incomplete Outcome Data Reason	Selective Outcome Reporting Judgement	Selective Outcome Reporting Reason	Major Baseline Imbalance Judgement	Major Baseline Imbalance Reason	Serious AE Definitions Judgement	Serious AE Definitions Reason	Method of AE Monitoring Judgement	Method of AE Monitoring Reason
Marinez-Taboada 2008	High Risk of Bias	only 50% remained in Tx group and 22% in placebo	Low Risk of Bias	Prespecified outcomes in methods reported in results	High Risk of Bias	Comorbidities and laboratory findings significantly different in both group at baseline	Low Risk of Bias	As stated above, adverse events were recorded at each visit. A serious adverse event was defined as an event that was fatal, life-threatening, required hospitalisation or extension of existing hospitalisation, resulted in persistent or substantial disability or incapacity, or was medically significant or required intervention to prevent any of the outcomes mentioned.	Low Risk of Bias	Clinical evaluations were performed at screening, baseline and every 2 weeks during the first 3 months of treatment, then monthly thereafter
Pavelka 2009	Low Risk of Bias	approximately 20% dropout in both group and last observation carry forward method used to treat missing data	High Risk of Bias	No mention of adverse events as an outcome	Low Risk of Bias	no major baseline imbalances observed	Unclear	not sufficient evidence to make judgement	Unclear	not sufficient information to make judgement
van den Bosch 2002	Unclear	no mention of total patient loss	Low Risk of Bias	Prespecified outcomes in methods reported in results	Low Risk of Bias	No significant baseline imbalance observed	Unclear	No definition stated	Low Risk of Bias	AE routinely followed
van der Heijde 2007	High Risk of Bias	less than 80% completion	High Risk of Bias	important side effects such as TB, opportunistic infections missing	Unclear	No baseline measures reported	Unclear	no AE definition stated	Low Risk of Bias	Safety assessments, including treatment-emergent adverse events (AEs), serious AEs, and serious and medically important infections, were based on reports of AEs and results of routine physical examinations and laboratory determinations
van der Vaart 2005	Low Risk of Bias	No dropout or loss to follow-up	Unclear	No mention of adverse events as an outcome	Low Risk of Bias	No significant baseline imbalance observed	Unclear	no AE definition stated	Low Risk of Bias	At each visit, the following question was asked to evaluate adverse events: "Did you have any complaints (especially fever, or extra or new symptoms) since the last visit?"
Westhovens 2006	Unclear	intention to treat population used for safety analysis	Low Risk of Bias	Prespecified outcomes in methods reported in results	Low Risk of Bias	No significant baseline imbalance observed	Low Risk of Bias	A serious infection was defined as any infection identified by the investigator on the basis of clinical judgment or the results of culture, microscopy, serology/biopsy, or imaging that also met the definition of a serious adverse event. A serious adverse event (as defined by the International Conference on Harmonization guidelines) was any adverse event that resulted in death, was life threatening, resulted in hospitalization or prolongation of hospitalization, caused persistent or substantial disability, or resulted in a congenital anomaly or birth defect	Low Risk of Bias	Safety evaluations included assessments of adverse events, measurements of vital signs, and the results of routine laboratory tests
van de Kerkhof 2008	Low Risk of Bias	89% complete 12 weeks	High Risk of Bias	safety only reported in >3% cases	Low Risk of Bias	no significant baseline imbalance observed	Unclear	not stated	Low Risk of Bias	Safety was assessed throughout the study
Monk 2006	High Risk of Bias	50% completion in bio group			Unclear	not described	Low Risk of Bias	Toxicities are reported as per National Cancer Institute Common Toxicity Criteria version 2.0	Low Risk of Bias	AE monitored routinely (weekly)
Uppal 2009	High Risk of Bias	5/9 Tx and 6/18 in Pb	High Risk of Bias	reported only on those who did not drop out even in baseline characteristics	Low Risk of Bias	No significant baseline imbalance observed	Unclear	not stated	Unclear	patients routinely monitored for AE
Aviles 2007b	Low Risk of Bias	No missing outcome data	Low Risk of Bias	All outcomes were reported	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	High Risk of Bias	Just report AE as they arise
Braun 2002	Low Risk of Bias	No missing outcome data	Low Risk of Bias	All outcomes are prespecified according to surveys and endpt defined	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	Low Risk of Bias	Surveys at week 0, 2, 6, 12
Fleischmann 2003	Low Risk of Bias	No missing outcome data	Low Risk of Bias	well defined outcomes	Low Risk of Bias	Characteristics between 2 groups appear similar	Low Risk of Bias	define AE based on WHO dictionary	Low Risk of Bias	Study determined safety of this drug
Gottlieb 2004	Low Risk of Bias	No missing outcome data	Low Risk of Bias	well defined outcomes	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	High Risk of Bias	Just report AE as they arise
Freedman 2009	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Disease response was defined using modified International Workshop Group response criteria.	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	High Risk of Bias	Report AE as they occur
Pescovitz 2009	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes defined	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	High Risk of Bias	Report AE as they occur
Rau 2004	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes defined by scale	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	Low Risk of Bias	Adverse event (AE) assessments were conducted at screening, baseline, and at every study evaluation.
Sany 2005	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes have been pre-defined	High Risk of Bias	Fewer women in the placebo group	Low Risk of Bias	AE have been predefined	Low Risk of Bias	Form given to record symptoms of AE
Schreiber 2005	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes assessed by standard survey	Low Risk of Bias	Generally well balanced	Unclear	Does not define AE	Low Risk of Bias	AE were constantly monitored
Schreiber 2007	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes assessed by standard survey	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	Low Risk of Bias	AE were constantly monitored

STUDY	Incomplete Outcome Data Judgement	Incomplete Outcome Data Reason	Selective Outcome Reporting Judgement	Selective Outcome Reporting Reason	Major Baseline Imbalance Judgement	Major Baseline Imbalance Reason	Serious AE Definitions Judgement	Serious AE Definitions Reason	Method of AE Monitoring Judgement	Method of AE Monitoring Reason
Westhovens 2009	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes defined by scale	Low Risk of Bias	Characteristics between 2 groups appear similar	Low Risk of Bias	Adverse events and serious adverse events were classified using the Medical Dictionary for Regulatory Activities version 10.1.	Low Risk of Bias	AE were constantly monitored
Witzig 2002	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes are defined	Low Risk of Bias	Characteristics between 2 groups appear similar	Unclear	Does not define AE	High Risk of Bias	Report AE as they occur
Zhou 2007	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Outcomes are defined	High Risk of Bias	Differences in age, gender, race,	Unclear	Does not define AE	Low Risk of Bias	Actively monitor AE
Boetticher 2008	Low Risk of Bias	Two from each group excluded. Authors did a "per protocol" analysis.	Low Risk of Bias	Protocol not available but likely all major outcomes reported	Low Risk of Bias	Table 2, balanced baseline characteristics	Low Risk of Bias	Refer table 6	Low Risk of Bias	"Patients were evaluated in person or by phone visit by a nurse coordinator or co-investigator on days 1, 4, 8, 11, 15, and 18, as well as at 1, 3, and 6 months."
Chung 2003	Low Risk of Bias	1 in the placebo, 5 in the 10mg/kg and 1 in the 5 mg/kg group did not receive all infusions but the authors appear to have included them properly in the analysis.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Table 1, balanced baseline characteristics	Unclear	All reported without a priori labelling of serious AEs.	Low Risk of Bias	At each visit, patients were queried about the occurrence of adverse effects.
Cohen 2002	Unclear	Drop-out rate ranged from 19 to 26% across groups. Drop-out rates and reasons for withdrawals were reported but missing data were not imputed for efficacy.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Balanced baseline characteristics	Unclear	No definition of SAE's	Low Risk of Bias	Safety assessments done at each follow-up.
Coplan 2009	Low Risk of Bias	Withdrawals reported.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Balanced baseline characteristics	Unclear	No definition of SAE's	Unclear	Not reported.
Furst 2003	Low Risk of Bias	Low-drop out rate and reasons reported.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Balanced baseline characteristics	Low Risk of Bias	Serious infection defined as 'requiring intravenous antibiotics or hospitalization'	Unclear	Method not reported.
Griffiths 2010	Low Risk of Bias	Drop-outs accounted for.	Low Risk of Bias	The defined primary and secondary end points were reported	Low Risk of Bias	Balanced baseline characteristics	Low Risk of Bias	Major CV events defined and judged by independent cardiologist	Low Risk of Bias	Safety was evaluated by assessing adverse events and routine hematologic and laboratory values.
Hauser 2008	Low Risk of Bias	16% withdrew from Rituximab and 40% withdrew from Placebo. Reasons given.	Low Risk of Bias	Primary and secondary end points reported	Low Risk of Bias	Balanced baseline characteristics	Low Risk of Bias	See Table 4.	Low Risk of Bias	Regularly assessed.
Herold 2000	Unclear	Primary outcomes were given but no description on withdrawals or drop-outs	Low Risk of Bias	Outcome of interest were acute adverse events. These were given	Unclear	No info on demographics, just mention that they are comparable groups	Low Risk of Bias	Adverse events classified according to the Common Toxicity Criteria (CTC) grading system for cancer.	Unclear	Not clearly reported.
Johnsen 2006	Low Risk of Bias	Reasons for withdrawals were reported and missing data imputed appropriately.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Balanced baseline characteristics	Low Risk of Bias	Defined in Table 4.	Unclear	Not reported.
Sandborn 2009	Low Risk of Bias	All randomised patients included in safety analysis.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Table 1, balanced baseline characteristics	Unclear	Not defined a priori.	Low Risk of Bias	Monitored to 54 weeks.
Schiff 2004	Low Risk of Bias	All patients included in safety analysis.	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Table 1, balanced baseline characteristics	Low Risk of Bias	Defined in methods using WHO terminology	Low Risk of Bias	Adverse events assessed at every visit
Van der Heijde 2006	Low Risk of Bias	Double-blind' but not reported who was blinded	Low Risk of Bias	Important outcomes reported	Low Risk of Bias	Table 1, balanced baseline characteristics	Unclear	Not defined	Low Risk of Bias	Patients monitored during follow-ups
van Vollenhoven 2009	Low Risk of Bias	Withdrawals included in analysis, as non-responders	Low Risk of Bias	Primary and secondary endpoints given	Low Risk of Bias	Table 1, balanced baseline characteristics	Unclear	not described	Unclear	not reported
Weinblatt 1999	Low Risk of Bias	All randomized patients included in analysis	Low Risk of Bias	Primary and secondary endpoints given	Low Risk of Bias	Imbalance in gender (slightly). Receiving DMARDs other than MTX at screening, Mean duration of MTX therapy	Unclear	Not defined	Low Risk of Bias	AE's graded using National Cancer Institute criteria
Menter 2008	High Risk of Bias	Total number who received adalimumab not clearly reported	Low Risk of Bias		Low Risk of Bias	Balanced baseline characteristics	Unclear	Not defined a priori: some defined in results section	Low Risk of Bias	AE data were collected throughout the study and 70 days after the last dose
Weinblatt 2008	Low Risk of Bias	No missing outcome data	Low Risk of Bias	Uses Score and outcomes defined previously	High Risk of Bias	More women in treatment group than placebo	Low Risk of Bias	Definitions of AE were previously defined	Low Risk of Bias	Patients were monitored
Cassano 2006	Low Risk of Bias	page 226, right column: ... four patients were not included in the efficacy analysis...	Low Risk of Bias	Page 226, right column: Clinical assessment was performed at baseline, after 4 weeks and after 12 weeks(end of study) and PASI was calculated...	Low Risk of Bias	page 226, right column: The two treatment groups were homogenous as no significant differences of baseline parameters were detected between the two arms.	Unclear	no explicit definition	Low Risk of Bias	page 226, left column: ...whereas the Dermatology Life Quality index (DLQI) was used to evaluate the impact on quality of life. Routine laboratory examinations were done at baseline and weeks 12...
Jones 2008	Low Risk of Bias	greater than 80% follow up in each gp	Low Risk of Bias	Uses Score and outcomes defined previously	Low Risk of Bias	Similar baselines	Unclear	No definitions of AE	Low Risk of Bias	Patients were monitored for AE, SAE, withdrawals due to AE, deaths