| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
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| Author, Year:Alonso-Ruiz et al., 2008205Country and setting:MultinationalFunding:NRAims of Review:To perform a systematic review of RCTs of anti-TNFα drugs inRA followed by a metaanalysis of the efficacy and safety of different doses of INF, ETN and ADAQuality Rating:Good | Study design:Systematic Review and meta-analysesNumber of Patients:7087Studies Included:N = 13 | Characteristics of Included Studies:RCTs of INF, ETN, or ADA of at least 6 months duration with efficacy measured by ACR responseCharacteristics of Included PopulationsPatients had to satisfy the ACR criteria for dianosis of RA and have active diseaseCharacteristics of Interventions:All were trials of INF, ETN, or ADA. 4 INF + MTX vs. MTX trials (INF doses ranged from 3 mg/kg to 10 mg/kg, administered every 8 wks; 1 trial included a 3 and 10 mg/kg arm administered every 4 wks too.)4 ETN trials: 1 ETN + MTX vs. MTX; 1 ETN vs. placebo; 1 ETN vs. MTX; 1 ETN + MTX vs. MTX vs. ETN (ETN doses were either 10 mg or 25 mg administered twice weekly)5 ADA trials: 2 ADA + MTX vs. MTX; 1 ADA vs. placebo; 1 ADA + DMARD vs. DMARD; 1 ADA + MTX vs. MTX vs. ADA (ADA doses were 20 mg or 40 mg adminstered once per wk or 2 wks; 1 trial included an 80 mg/2 wk arm) | Study Results:Any anti-TNFα drug (all doses) vs. control treatment (13 studies):ACR20: RR, 1.81 (95% CI, 1.43-2.29); NNT, 6 (5-7)ACR50: RR, 2.46 (95% CI, 1.75-3.45); NNT, 5 (5-6) ACR70: RR, 2.77 (95% CI, 1.85-4.15); NNT, 7 (7-9)Any anti-TNFα drug (recommended doses) vs. control treatment :ACR20: RR, 1.8 (95% CI, 1.4-2.3); NNT, 5 (5-6)ACR50: RR, 2.4 (95% CI, 1.7-3.4); NNT, 5 (5-6) ACR70: RR, 2.7 (95% CI, 1.8-4.1); NNT, 7 (7-9)ADA (all doses) vs. control treatmentACR20: RR, 1.9 (95% CI, 1.3-2.8); NNT, 6 (5-7)ACR50: RR, 2.7 (95% CI, 1.6-4.4); NNT, 6 (5-7)ACR70: RR, 3.3 (95% CI, 1.8-6.3); NNT, 9 (7-11)ADA (recommended doses) vs. control treatmentACR20: RR, 2.0 (95% CI, 1.3-2.9); NNT, 5 (4-6)ACR50: RR, 2.8 (95% CI, 1.6-4.7); NNT, 5 (5-6)ACR70: RR, 3.5 (95% CI, 1.9-6.7); NNT, 7 (6-8)ETN (all doses) vs. control treatmentACR20: RR, 1.7 (95% CI, 1.1-2.6); NNT, 7 (5-10)ACR50: RR, 2.1 (95% CI, 1.1-3.9); NNT, 6 (5-9)ACR70: RR, 2.0 (95% CI, 0.9-4.4); NNT, NSETN (recommended doses) vs. control treatmentACR20: RR, 1.7 (95% CI, 1.1-2.7); NNT, 6 (5-8)ACR50: RR, 2.2 (95% CI, 1.1-4.3); NNT, 6 (4-7)ACR70: RR, 2.1 (95% CI, 0.9-4.5); NNT, NSINF (all doses) vs. control treatmentACR20: RR, 1.8 (95% CI, 1.2-2.8); NNT, 5 (4-6)ACR50: RR, 2.6 (95% CI, 1.5-4.7); NNT, 5 (5-6)ACR70: RR, 2.9 (95% CI, 1.4-5.8); NNT, 8 (6-10)INF (recommended doses) vs. control treatmentACR20: RR, 1.7 (95% CI, 1.1-2.6); NNT, 5 (4-6)ACR50: RR, 2.2 (95% CI, 1.2-4.1); NNT, 6 (5-7)ACR70: RR, 2.4 (95% CI, 1.2-5.0); NNT, 9 (7-13)Efficacy of anti-TNFα drugs (recommended doses) in combination with MTX compared with MTX alone in patients with insufficient responses to MTXACR20: RR, 2 .6 (95% CI, 2.0 5-3.31)ACR50: RR, 4 .13 (95% CI, 2.59-6 .59)ACR70: RR, 4.14 (95% CI, 2.43-7.05)Efficacy of anti-TNFα drugs (recommended doses) plus MTX compared to MTX alone in patients with no previous resistance to MTXACR20: RR, 1.15 (95% CI, 1.07-1.22)ACR50: RR, 1.56 (95% CI, 1.41-1.72)ACR70: RR, 1.77 (95% CI, 1.52-2.05) | Adverse Events:Any anti-TNFα drug vs. control treatmentWithdrawal due to adverse event: RR, 1.25 (95% CI, 0.65-2.39); NNH, NSTotal adverse event: RR, 1.0 (1.0-1.5); NNH 27 (17-59)Serious adverse event: RR, 1.1 (0.8-1.6); NNH, NSInfections: RR, 1.9 (0.9-1.2); NNH, NSSerious infections: RR, 1.4 (0.8-2.2) NNH, NSInfusion Reactions: RR, 3.0 (1.0-8.6); NNH, 8 (7-10)Malignancies: RR, 1.5 (0.8-3.0); NNH, NSMortality: RR, 0.8 (0.3-2.1); NNH, NSADA vs. control treatmentWithdrawal due to adverse event: RR, 1.4 (1.0-2.0); NNH, 47 (26-251)Total adverse event: RR, 1.1 (0.9-1.1); NNH, NSSerious adverse event: RR, 1.0 (0.7-1.4); NNH, NSInfections: RR, 1.1 (0.9-1.2); NNH, NSSerious infections: RR, 1.2 (0.6-2.8); NNH, NSInfusion Reactions: RR, 2.7 (1.7-4.2); NNH, 9 (7-14)Malignancies: RR, 1.1 (0.4-2.7); NNH, NSMortality: RR, 1.3 (0.4-4.7); NNH, NSETN vs. control treatmentWithdrawal due to adverse event: RR, 0.7(0.5-0.9); NNH, -26 (-143 to -14) Total adverse event: RR, 1.0 (0.9-1.1); NNH, NSSerious adverse event: RR, 0.9 (0.5-1.6); NNH, NS Infections: RR, 1.0 (0.9-1.0); NNH, NSSerious infections: RR, 0.9 (0.4-2.3); NNH, NS Infusion Reactions: RR, 5.1 (2.9-8.8); NNH, 5(4-6)Malignancies: RR, 1.9 (0.6-5.7); NNH, NS Mortality: RR, 1.5 (0.2-9.5); NNH, NSINF vs. control treatmentWithdrawal due to adverse event: RR, 2.0 (1.3-3.1); NNH, 24 (17-41)Total adverse event: RR, 1.0 (0.9-1.0); NNH, NS Serious adverse event: RR, 1.4 (1.0-2.0); NNH, 31 (17-167)Infections: RR, 1.2 (1.1-1.3); NNH, 10 (7-24)Serious infections: RR, 1.8 (0.9-3.4); NNH, NS Infusion Reactions: RR, 2.7 (1.7-4.2); NNH, 9 (7-14) Malignancies: RR, 2.6 (0.6-11.6); NNH, NSMortality: RR, 0.5 (0.2-1.4); NNH, NS |

| **Study Characteristics, Quality Rating** | **Study Information** | **Study Characteristics**  | **Results** | **Adverse Events** |
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| Author, Year:Bergman et al., 2010206Country and setting:MultinationalFunding:Hoffmann La-RocheAims of Review:ACR response between TCZ and other biologic agents in patients with rheumatoid arthritis who have inadequate response to disease-modifying antirheumatic drugsQuality Rating:Fair | Study design:Systematic review and meta-analysisNumber of Patients:10,419Studies Included:N = 18 | Characteristics of Included Studies:Double-blind, randomized, placebo controlled trials, 24 to 30 weeksCharacteristics of Included PopulationsAdults with RACharacteristics of Interventions:RCTs - study duration of at least 6 months; | Study Results:Fixed-Effects Model Relative Risk (95% CrI) / Random-Effects Model Relative Risk (95% CrI)Biologic agent vs.placebo, Fixed-Effects Model Relative Risk (95% CrI) ACR20TCZ: 2.0 (1.9-2.2) TNF- inhibitors :1.9 (1.7-2.1) ABA: 1.9 (1.7-2.1) RTX: 1.8 (1.5-2.2) ACR50TCZ: 3.5 (3.0, 4.0)TNF- inhibitors: 2.8 (2.4, 3.2)ABA: 2.7 (2.2, 3.3)RTX: 2.8 (1.8, 4.0)ACR70TCZ: 6.8 (4.9, 9.4)TNF- inhibitors: 3.8 (3.1, 4.8)ABA: 3.4 (2.5, 4.8)RTX: 4.3 (2.2, 8.9)Biologic agent vs.placebo, Random-Effects Model Relative Risk (95% CrI)ACR20TCZ: 2.1 (1.6-2.5)TNF:- inhibitors: 2.0 (1.7-2.3)ABA: 1.9 (1.4-2.3)RTX: 1.9 (1.3-2.5)ACR50TCZ: 3.6 (2.5, 5.0)TNF- inhibitors: 3.2 (2.5, 4.3)ABA: 2.7 (1.7, 4.0)RTX: 2.9 (1.5, 4.9)ACR70TCZ: 6.9 (4.5, 10.8)TNF- inhibitors: 4.0 (3.0, 6.0)ABA: 3.6 (2.2, 6.2)RTX: 4.4 (1.9, 10.5)Pairwise comparison of biologic agentsACR20TCZ vs.TNF- inhibitors 1.1 (1.0, 1.2) / 1.1 (0.8, 1.3)TCZ vs.ABA 1.1 (1.0, 1.2) / 1.1 (0.8, 1.6)TCZ vs.RTX 1.1 (0.9, 1.4) / 1.1 (0.8, 1.7)ABA vs.TNF- inhibitors 1.0 (0.9, 1.1) / 0.9 (0.7, 1.2)RTX vs.TNF- inhibitors 1.0 (0.8, 1.2) / 1.0 (0.6, 1.3)RTX vs.ABA 1.0 (0.8, 1.2) / 1.0 (0.7, 1.5)ACR50TCZ vs.TNF- inhibitors 1.3 (1.1, 1.5) / 1.1 (0.7, 1.6)TCZ vs.ABA 1.3 (1.0, 1.6) / 1.3 (0.8, 2.3)TCZ vs.RTX 1.3 (0.9, 1.9) / 1.2 (0.7, 2.5)ABA vs.TNF- inhibitors 1.0 (0.8, 1.2) / 0.9 (0.5, 1.3)RTX vs.TNF- inhibitors 1.0 (0.7, 1.5) / 0.9 (0.5, 1.6)RTX vs.ABA 1.0 (0.7, 1.5) / 1.1 (0.5, 2.1)ACR70TCZ vs.TNF- inhibitors 1.8 (1.2, 2.6) / 1.7 (1.0, 2.8)TCZ vs.ABA 2.0 (1.3, 3.1) / 1.9 (1.0, 3.6)TCZ vs.RTX 1.6 (0.7, 3.3) / 1.6 (0.6, 4.0)ABA vs.TNF- inhibitors 0.9 (0.6, 1.2) / 0.9 (0.5, 1.5)RTX vs.TNF- inhibitors 1.1 (0.5, 2.4) / 1.1 (0.4, 2.6)RTX vs.ABA 1.3 (0.6, 2.8) / 1.2 (0.5, 3.2) | Adverse Events:NA |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Bernatsky et al., 2010207Country and setting:Study conducted in Canada - components are multinationalsFunding:NRAims of Review:a systematic review and synthesis of observational studies of TNF antagonists andinfection risk.Quality Rating:Fair | Study design:Systematic review and meta-analysisNumber of Patients:NRStudies Included:N = 7 | Characteristics of Included Studies:5 cohort and 2 nested case-control studiesCharacteristics of Included PopulationsPatients with RA and serious infectionsCharacteristics of Interventions:Anti-TNFs | Study Results:Anti-TNF therapy appeared to significantly increase risk of serious infection (pooled adjusted RR1.37, 95% CI, 1.18-1.60). | Adverse Events:The summary RR, suggested about a 40% increased risk of serious infections in patients with RA exposed to TNF antagonists (RR, 1.37; 95% CI, 1.18-1.60). |

| Study Characteristics  | Characteristics of Included Studies  | Results | Adverse Events | Assessments, Study Appraisals, and Quality Rating |
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| Author, year, country, funding:Bongartz, 2006, multinational, Mayo foundation, Abbott & Centocor208Study Design:Systematic literature search with meta-analysisAims of the Review:* To assess extent to which anti-TNF antibody therapy may increase risk of serious infection and malignancies in pts with RA by performing a meta-analysis
* To derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy

Number of Pts:5014 (9 trials) | Studies included:* Keystone (2004)
* St Clair (2004)
* Furst (2003)
* Lipsky (2000)
* van de Putte (2003)
* Weinblatt (2003)
* Maini (1998)
* van de Putte (2004)
* Westhovens (2004)

Charac**t**eristics of included studies:* RCTs of INF and ADA in which pts had ACR-diagnosed RA and were randomized to anti-TNF vs. placebo (or anti-TNF antibody + traditional DMARD vs. placebo + traditional DMARD)
* Both pt and observer were masked
* Trial had to be at least 12 wks in duration

Characteristics of included populations:* Pts with an ACR diagnosis of RA who were randomized to receive Anti-TNF or placebo

Characteristics of interventions:Anti-TNF (dosing varied) or Control | * In pts with RA, anti-TNF treatment leads to increased risk of serious infections and a dose-dependent increased risk of malignancies. Serious infections reported in 126 anti-TNF- treated pts vs. 26 control group pts (OR, 2.0; 95% CI, 1.3-3.1)
* Malignancies reported in 24 / 3493 (0.8%) pts who received > 1 dose of anti-TNF vs. 2 / 1512 (0.2%) pts on control
* Pooled OR for malignancies in anti-TNF group vs. placebo group: 3.3 (95% CI, 1.2-9.1)
* Number needed to harm was 154 (95% CI 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (39-125) within a treatment period of 3 to 12 months
 | Overall AEs reported: * Malignancy: Anti-TNF (23/3192)Control (3/1428) OR: 3.3 (95% CI 1.2 – 9.1)
* Serious Infections: Anti-TNF (126/3493)Control (26/1512) OR: 2.0 (1.3-3.1)
 | Publication Bias Assessed:Not reportedHeterogeneity Assessed:YesStandard Method of Study Appraisals:YesComprehensive Search Strategy:Yes - briefly describe in box: EMBASE, MEDLINE, Cochrane Library, and electronic abstracts of the annual scientific meetings both the European League Against Rheumatism and the American College of Rheumatology – through December 2005Quality Rating: Fair |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Bongartz et al., 2009209Country and setting:MultinationalFunding:WyethAims of Review:To assess the risk of malignancy with ETNQuality Rating:Good | Study design:Systematic review and meta-analysisNumber of Patients:3316 patients, 2244 who received ETN (contributing 2484 person-years of follow-up) and 1072 who received control therapy (1051 person-years).Studies Included:N = 9 (8 published, 1 unpublished) | Characteristics of Included Studies:RCTS at least 12 weeks longCharacteristics of Included PopulationsPatients with RACharacteristics of Interventions:ETA vs. Control | Study Results: | Adverse Events:Malignancies in 26 patients in the ETN group (incidence rate (IR) 10.47/1000 person-years) and 7 in the control group (IR 6.66/1000 person-years). A Cox’s proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI, 0.79-4.28) for the ETN group compared with the control group. |

| Study Characteristics | Characteristics of Included Studies | Results | Adverse Events | Assessments, Study Appraisals, and Quality Rating |
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| Author, year, country, funding:Clark, 2004210, International: Europe, U.S., Canada, Australia, Health Technology Assessment Programme (U.K.)Study Design:Systematic review and meta-analysis analysisAims of Review:To review evidence on clinical benefits, hazards, and cost-effectiveness of AKA in adult RA ptsNumber of Pts:2,905 | Studies included:Efficacy Trials: * Bresnihan (1998)
* Cohen (2001)
* Cohen (2002)
* Unpublished report by Amgen (2001; STN 103950 Clinical Review; low-dose for 3 mos)

Safety Trial: * Fleischmann (2001)

Characteristics of included studies:* RCTs (except 1) of AKA or AKA + MTX in pts with highly active RA
* Fleischmann control arm consisted of placebo + DMARD txt

Characteristics of included populations:* Mean ages 50s
* Duration 6 mos to 10 yrs
* Majority had failed at least 1 DMARD and some were taking MTX up to trial start
* Majority taking low-dose steroids and NSAIDs

Characteristics of interventions:* AKA alone:
* AKA from 2.5 mg/day to 150 mg/day
* AKA + MTX: AKA 0.04 mg/kg per day to 2.0 mg/kg per day or fixed dose 100 mg/day
 | Adjusted indirect comparisons with anti TNF agents (ETN, INF) suggested that AKA may be significantly less effective at relieving clinical symptoms than anti-TNF agents (-0.21; 95% CI, -0.32 to -0.10) Adjusted indirect comparisons:* RD (95% CI)
* TNF+MTX vs. MTX 0.37 (0.28 to 0.45)
* AKA+MTX vs. MTX 0.16 (0.09 to 0.23)
* AKA+MTX vs. TNF+MTX -0.21 (-0.32 to -0.10)
 | Withdrawals due to adverse events: * Control: 4.1% to 9%
* AKA: 5% to 13%

Specific adverse events: * SAEs:Control: 3.2% to 11.6%AKA: 4.4% to 12.8%
* Malignancy: Control: 0% to 1.8%AKA: 0% to 1.1%
* Injection Site Reactions: Control: 3% (low-dose study) to 33%AKA: 19.8% (low-dose study) to 73%
* Any infection: Control: 13.3% (low-dose study) to 50%AKA: 13.5% (low-dose study) to 48.4%
* Serious infections: Control: 0.4% to 1.4%AKA: 0.8% to 2.1%
* Neutropenia: Control: 0% to 4%AKA: 0% to 9%
* Antibodies to IL-1Ra: Control: 0% to 1.8%AKA: 0.9% to 5%
 | Publication Bias Assessed:NRHeterogeneity Assessed: YesStandard Method of Study Appraisals:YesComprehensive Search Strategy:Yes Quality Rating: Good |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Devine et al., 2011211Country and setting:MultinationalFunding:NRAims of Review:efficacy of biologic disease-modifyingantirheumatic drugs (DMARDs) vs.placebo with or withoutMTX, in treating rheumatoid arthritis.Quality Rating:Fair | Study design:Systematic review and meta-analysisNumber of Patients:6 months: 11,58912 months: 6051Studies Included:6 months: 23 RCTs12 months: 10 RCTs | Characteristics of Included Studies:RCTs at least 22 weeks outcomesCharacteristics of Included PopulationsPatients with RA and and patient populations defined as DMARD-IR or MTX (MTX)-inadequate respondersCharacteristics of Interventions:Biologic DMARDs with or without MTX or other nonbiologic DMARDs, compared with placebo with or without MTX or other nonbiologic DMARDs | Study Results:Log Odds Ratio Estimates for the 6-Month and 12-Month Models by Drug6-month modelCertolizumab μ1 2.60 0.44 1.83-3.59 1TCZ μ2 1.67 0.19 1.31-2.07 2RTX μ3 1.61 0.59 0.55-2.85 3INF μ4 1.57 0.27 1.03-2.10 4ETN μ5 1.43 0.25 1.00-2.00 5ADA μ6 1.37 0.22 0.94-1.83 6GOL μ7 1.36 0.38 0.64-2.14 7ABA μ8 1.16 0.27 0.61-1.68 8ANK μ9 0.98 0.28 0.47-1.58 9MTX 0.78 0.19 0.39-1.17Baseline disease duration 1 0.08 0.04 < 0.01-0.18Baseline HAQ score 2 -0.45 0.53 -1.49-0.63Variance 2 0.05 0.02 < 0.01-0.2812-month modelCertolizumab μ1 2.02 0.44 1.16-2.83 1RTX μ2 1.95 0.90 0.47-4.00 2ADA μ3 1.37 0.28 0.83-1.89 3INF μ4 1.36 0.31 0.80-1.99 4ETN μ5 0.86 0.32 0.28-1.43 5ABA μ6 0.63 0.30 0.08-1.24 6MTX 0.84 0.21 0.42-1.26Baseline disease duration 1 0.10 0.04 < 0.01-0.17Baseline HAQ score 2 0.46 0.78 -1.11-1.89Variance 2 0.02 0.06 < 0.01-0.88 | Adverse Events:NR |

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| Study Characteristics  | Characteristics of Included Studies  | Results | Adverse Events | Assessments, Study Appraisals, and Quality Rating |
| Author, year, country, funding:Gartlehner et al., 2006212USStudy Design:META-ANALYSISanalysis (random effects model); systematic reviewAims of the Review:To assess comparative efficacy and safety of biologic agents for RANumber of Patients:ADA: 2,354ETN: 1,151INF: 704AKA:1,039 (#'s refer to 17 sudies used for adjusted indirect comparisons of efficacy) | Studies included:* 26 controlled trials
* 18 additional studies assessed safety

Characteristics of included studies:* Often limited to 1 year of follow-up
* Reported on DAS-28
* Radiographic progression, functional capacity, and QOL

Characteristics of included populations:* Narrowly defined populations
* Mean age 53.4
* 76% female
* 89% caucasion

Characteristics of interventions:* All efficacy studies except 1 were funded by the pharmaceutical industry
* All 12 weeks plus of duration (for observational studies it was 3 months or greater and 100 or more patients)
 | Adjusted indirect comparison indicate no significant differences in efficacy between antiTNF drugs* Anti-TNF drugs appear to be more efficacious than AKA but do not differ among each other. Inddirect comparisons of INF and of anti-TNF drugs as a class compared to AKA yielded a statistically significant greater efficacy on ACR 20 [RR 0.58 (95%CI 0.38-0.90) and RR 0.61 (95% CI 0.39-0.96), respectively], but not ACR 50
* Few studies assessed longterm radiographic outcomes. In general, rate of radiographic progression was significantly lower in patients treated with biologics than in placebo-treated patients, regardless of concomitant DMARD therapy. Similarly, QoL improved significantly for patients treated with biologics
 | Because of lack of sound long-term safety data, evidence is insufficient to draw firm conclusions about comparative safety of biologics* Higher rates of injection site reactions for AKA than ADA and ETN (56% vs. 19% vs. 25%)
 | Publication Bias Assessed:YesHeterogeneity Assessed:YesStandard Method of Study Appraisals:YesComprehensive Search Strategy:Yes - briefly describe in box: Searched Medline, Embase, Cochrane and International Pharmaceutical Abstracts from 1980-2006. Also explored CDER database.Quality Rating: Good |

| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
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| Author, Year:Gaujoux-Viala et al., 2010213Country and setting:NRFunding:NRAims of Review:To analyze the literature on the efficacy on signs and symptoms, disability and structure, of oral DMARDS and to assess safety, with a special focus on cancers and infectionsQuality Rating:Fair | Study design:Systematic Review and Meta-analysisNumber of Patients:Efficacy studies: 14, 159Adverse event studies: NAStudies Included:Efficacy studies: 97Safety studies: 39 | Characteristics of Included Studies:RCTs reporting the efficacy on signs and symptoms, disability and/or structure of oral DMARDs vs.placebo (except for MTX) or other nonbiologic DMARDs, in patients with RA\*from online supplemental materialCharacteristics of Included PopulationsPatients with RACharacteristics of Interventions:MTX: * 17 studies
* 4,147 patients
* age: 49.7±3.4
* % female: 72.4
* disease duration, yrs: 6.7±4.5

LEF:* 9 studies
* 3,617 patients
* age: 54.3±4.2
* % female: 74.5
* disease duration, yrs: 6.3±2.5

SSZ: * 22 trials
* 2,813 patients
* age: 52.1±4.0
* % female: 68.8
* disease duration, yrs: 5.6 ± 3.6

Hydroxychloroquine: * 20 studies
* 2,182 patients
* age: 45.5±6.0
* % female: 73.5
* disease duration, yrs: 3.8±3.0
 | Study Results:MTX vs. LEFSJC (4 studies, 1889 patients): Standardized Response Mean (SRM), 0.09 (95% CI, −0.12-0.30)Pain (4 studies, 1475 patients): SRM, −0.04 (95% CI, −0.33-0.26)Disability (4 studies, 1,465 patients): SRM, −0.09 (95% CI, −0.30-0.11) ACR20 response (4 studies, 1889 patients): OR, 1.04 (95% CI, 0.60-1.79)Structure (2 studies, 895 patients): SRM, 0.03 (95% CI, −0.10-0.16)MTX vs. SSZSJC (2 studies, 206 patients): SRM, 0.59 (95% CI, −1.96-3.15)Disability (2 studies,208 patients): SRM, 0.62 (95% CI, −0.86-2.10) ACR50 response (2 studies, 193 patients): OR, 1.57 (95% CI, 0.82-3.00)MTX monotherapy vs. MTX combo, DMARD naive No significant advantage of combo with MTX vs.MTX monotherapy for pain, Health Assessment Questionnaire, or ACR20, 50, or 70ACR20: OR, 0.53 (95% CI, 0.21-1.33)* MTX monotherapy vs. MTX combos, DMARD inadequate responders
* SJC (3 studies): SRM, −0.78 (95% CI, −1.30 to −0.25)
* Pain (3 studies): SRM, −0.64 (95% CI, −1.01 to −0.28)
* HAQ (3 studies) SRM, −1.21 (95% CI, −2.07 to −0.36)

ACR20 (2 studies): RR, = 0.26 (95% CI, 0.16 to 0.40)SSZ monotherapy vs. SSZ comboIn 6 trials (657 patients), no significant difference for SJC, function, or ACR20, 50 or 70. Significant finding: Structural damage (1 trial) favoring the combination MTX+SSZ+hydroxychloro-quine: SRM, −1.70 (95% CI, −2.03 to −1.37)25 Pain (1 trial) favoring SSZ monotherapy: SRM, 4.10 (95% CI, 2.91-5.29) | Adverse Events:MTX monotherapy vs. MTX combo, DMARD naïveWithdrawals due to lack of efficacy or toxicity were similar in both groups: RR, 1.16 (95% CI, 0.70-1.93)MTX monotherapy vs. MTX combos, DMARD inadequate responders8 trials show insignificant differences in withdrawals between MTX combo and monotherapy. One exception: O’Dell’s study of 102 DMARD inadequate responders. The combo of MTX + SSZ and hydroxychloroquine showed fewer withdrawals than MTX alone: RR, 0.30 (95% CI, 0.14 to 0.65). |

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| Study Characteristics  | Characteristics of Included Studies  | Results | Adverse Events | Assessments, Study Appraisals, and Quality Rating |
| Author, year, country, funding:Hochberg et al., 2003214MultinationalNRStudy Design:Systematic review and indirect comparisonsAims of the Review:Differences in efficacy of TNF alpha blocking agents, as measured by rate ratios for American College of Rheumatology (ACR) 20/50/70 responses, in patients with RA with an incomplete response to methotrexate.Number of Patients:1053380 placebo673 active | Studies included:* Maini et al. 1999
* Lipsky et al. 2000
* Weinblatt et al 1999
* Weinblatt et al. 2003

Characteristics of included studies:Placebo controlled, double blind, randomised clinical trials of at least 24 weeks’Characteristics of included populations:NR- assuming that it is adults with active RA with lack of response to MTXCharacteristics of interventions:the addition of TNF blocking agents (INF, ETN and ADA) to methotrexate in a "step-up" strategy  | Indirect comparisons, Relative Risk (95% CI)* ETNnercept vs. adalimumab ACR 20 1.10 (0.57 to 2.12) 2.60 (0.35 to 19.0)
* Infliximab vs. adalimumab 1.07 (0.66 to 1.73) 1.35 (0.47 to 3.85)
* ETNnercept vs. infliximab 1.03 (0.49 to 2.18) 1.92 (0.22 to 17.0)
 | NR | Publication Bias Assessed:NRHeterogeneity Assessed:YesStandard Method of Study Appraisals:NRComprehensive Search Strategy:Yes - briefly describe in boxQuality Rating: Fair |

| Study Characteristics | Study Design | ResultsAdverse Events  | Quality | Comments |
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| Author:Kirwan, 2009215Country and setting:Multi-nationalFunding:Chochrane Collaboration | Study design:Systematic Review and meta-analysesOverall study N:1414Study aims:To perform a systematic qualitative review of studies evaluating glucocorticoid efficacy in inhibiting the progression of radiological damage in rheumatoid arthritis. | Main results:* Comparison 1. Glucocorticoids vs. comparator
* Erosion outcomes refer to erosion scores expressed as percentage of max possible score for method used by individual studies.
* Outcome 1. SMD in progression of erosion scores = 0.40 in favor of glucocorticoids (95% CI 0.27, 0.54) (from abstract)
* Outcome 2. Change in erosions at 1 year as proportion of maximum score (N = 15, # of Participants = 1421) SMD = 0.39 (95% CI, 0.27, 0.52) in favor of glucocorticoids
* Outcome 3. Erosions at 1 year, data from 1 & 2 year studies (N = 10, # of partcipants = 940) SMD = -0.43 (95% CI, -0.62, -0.23) in favor of glucocorticoids
* Outcome 4> Erosions at 2 years, data from 1 & 2 year studies (N = 10, # of participants = 967) SMD = -0.40 (95% CI, -0.56, -0.24) in favor of glucocorticoids
* Outcome 5. Joint Space Narrowing at 1 year as a proportion of maximum score (n = 6, # of participants = 711) SMD = -0.27 (95% CI, -0.50, -0.04) in favor of glucocorticoids
* Outcome 6. Joint Space Narrowing at 2 years as a proportion of maximum score (N = 4, # of participants - 512) SMD = -0.31 -(95% CI, -0.51, -0.11) in favor of glucocorticoids
* Outcome 7. Joint Space Narrowing at 1 year data from 1 & 2 year studies (N = 4, # of participants = 473). SMD -0.22 (-0.51, 0.07)
* Outcome 8. Joint Space Narrowing at 2 years data from 1 & 2 year studies (N = 3, # of participants = 345) SMD = -0.28 (95% CI, -0.57, 0.01)
* Outcome 9. Proportion of patients progressing at year 1 (N = 4, # of participants = 261). Risk Ratio = 0.60 (95% CI, 0.48, 0.74), in favor of glucocorticoids

Adverse events:* NR
 | Review based on focused question of interest:YesDid search strategy employ comprehensive, systematic literature search?YesA search ofMEDLINE (from1966 to 22 February 2005) and Cochrane Central Register of Controlled Trials was undertaken, using terms ’corticosteroids’ and ’rheumatoid arthritis’ expanded according to Cochrane Collaboration recommendations. Identified abstracts were reviewed and appropriate reports obtained in full. Additional reports were identified from reference lists and from expert knowledge.Eligibility criteria clearly described?YesRandomized controlled or cross-over trials in adults with a diagnosis of rheumatoid arthritis in which prednisone or a similar glucocorticoid preparation was compared to either placebo controls or active controls (i.e. comparative studies) and where there was evaluation of radiographs of hands, or hands and feet, or feet by any standardised technique. Eligible studies had at least one treatment arm with glucocorticoids and one without glucocorticoids.Review studies independently reviewed by at least 2 persons?YesStandard method of critical appraisal before including?Yes | Comments:* Sensitivity analyses looked at several different ways of combining studies, and in all cases a similar benefit for glucocorticoid therapy was demonstrated (concomitant medication, length of study, when only low dose steroid studies were included, when step-down glucocorticoids were used, etc.)
* Total of 14 comparisons, each with multiple outcomes, reported in review. Comparison 1 was abstracted; others have not been abstracted. The comparisons are:

Comp 1. Glucocorticoids vs comparatorComp 2. Glucocorticoids + DMARD + NSAID vs DMARD + NSAIDComp 3. Glucocorticoids vs NSAIDComp 4. Oral low dose Glucocorticoids + DMARD + NSAID vs DMARD = NSAIDComp 5. Step down Glucocorticoids + DMARD + NSAID vs DMARD = NSAIDComp 6. Studies with less than 26 week of Glucocorticoid treatmentComp 7. Studies with more than 26 weeks of Glucocorticoid treatmentComp 8. Glucocorticoids vs comparator using modelled SDsComp 9. Glucocorticoids vs comparators using only studies with modelled SDsComp 10. Glucocorticoids vs. comparator using original SDs in studies with modelled SDsComp 11. Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed treatmentComp 12. Glucocorticoids vs. comparator sensitivity analyses by quality standards - Blinding of PatientsComp. 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to TreatComp 14. Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinded Assessors |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Kuriya et al., 2010216Country and setting:NRFunding:NRAims of Review:To examine the efficacy of MTX monotherapy compared withcombination therapy with a biologic when used as initial tx in early RA (ERA) pts.Quality Rating:Good | Study design:Systematic Review and Meta-analysisNumber of Patients:2,763Studies Included:N = 7 | Characteristics of Included Studies:Included studies were double-blind, randomised, active-comparator,controlled clinical trials that studied the efficacy of initial combination therapy (MTX + biologic) compared with MTX monotherapy in adult pts with clinically active ERACharacteristics of Included PopulationsPts were adults with clinically active ERA, defined as disease duration < 3 years, and with no or minimal previous exposure to MTX (≤ 4 weeks). Previous treatment with corticosteroids, SSZ or hydroxychloroquine/chloroquine was permitted.Characteristics of Interventions:3 INF trials: 3 mg/kg, q 8 weekly2 ADA trials: 40 mg, q 2 weekly1 ETN trial: 50 mg, q weekly1 ABA trial: 10 mg/kg, q 4 weekly | Study Results:Clinical Remission (Combo vs. Monotherapy, RR, (95% CI): 1.74 (1.54-1.98)Radiographic Non-progression (Combo vs. Monotherapy, RR, (95% CI): 1.30 (1.01-1.68) | Adverse Events:NA |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Leombruno et al., 2009217Country and setting:multi-nationalFunding:NRAims of Review:To evaluate the safety of biological treatments for RA using results from RCTsQuality Rating:Fair | Study design:Meta-analysisNumber of Patients:8,808Studies Included:N = 18 | Characteristics of Included Studies:The study must be an RCT with more than 30 patients randomly assigned to either an anti-TNF or a control group (non-DMARD or placebo) over a minimum of 10 wks. A Jadad score of ≥ 2 was required and tx arms of combination biological therapies were excluded.Characteristics of Included PopulationsPatients with RACharacteristics of Interventions:ADA: * 6 trials
* doses: 20-80 mg every wk or 20-80 mg every other wk
* all but 1 on background of MTX or other DMARD.

ETN: * 7 trials
* doses: 10-25 mg twice per wk
* 2 on background MTX
* 1 on background SSZ

INF: * 5 trials
* doses: 1-10 mg/kq every 4 wks or 3-10 mg/kg every 8 wks
* all on background of MTX
 | Study Results: | Adverse Events:Death, OR (CI) ADA: 2.04 (0.64 - 6.51)ETN: 2.34 (0.67 - 8.12) INF: 0.62 (0.21 - 1.79)Anti-TNF: 1.39 (0.74 - 2.62)Serious adverse events, OR (CI) ADA: 1.12 (0.86 - 1.45)ETN: 1.04 (0.73 - 1.47)INF: 1.17 (0.86 - 1.59)Anti-TNF: 1.11 (0.94 - 1.32)Serious infections, OR (CI) ADA: 1.53 (0.83 - 2.81)ETN: 0.89 (0.56 - 1.42)INF: 1.46 (0.86 - 2.47)Anti-TNF: 1.21 (0.89 - 1.63)Lymphomas, OR (CI) ADA: 1.07 (0.28 - 4.09)ETN: 1.42 (0.27 - 7.61)INF: 1.42 (.27 - 7.62)Anti-TNF: 1.26 (0.52 - 3.06)Non-cutaneous cancers and melanomas, OR (CI) ADA: 1.37 (0.49 - 3.89)ETN: 1.11 (0.42 - 2.96)INF: 1.70 (0.39 - 7.32)Anti-TNF: 1.31 (0.69 - 2.48)Non-melanoma skin cancers, OR (CI) ADA: 1.37 (0.49 - 3.89)ETN: 1.03 (0.38 - 2.77)INF: 1.70 (0.39 -7.32)Anti-TNF: 1.27 (0.67 - 2.42) |

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| Study Characteristics | Characteristics of Included Studies | Results | Adverse Events | Assessments, Study Appraisals, and Quality Rating |
| Author, year, country, funding:Maetzel, et al. 2000218 Multinational Arthritis and Autoimmunity Research Centre, Aventis Canada, Inc.Study Design:Meta-analysisAims of Review: To summarize evidence on treatment withdrawal rates reported in observational studies and RCTs of MTX, SSZ, HCQ (and parenteral gold) among RA patients. Number of Pts:Cannot determine | Studies included: 159 studies (71 RCTs, 88 observational studies) (159 satisfied screening criteria; 110 studies included in meta-analysis) Characteristics of included studies: Studies reporting information on number of patients withdrawingCharacteristics of included populations:RA Patients being treated with MTX, parenteral gold (GST), SSZ, and HCQCharacteristics of interventions:MTX, GST, SSZ, and HCQ | RA patients stay significantly longer on MTX than on other DMARDs. (Higher % stay on MTX vs. SSZ because of toxicity [RR 1.68, *P* < 0.0001]). Majority of withdrawals from SSZ and HCQ result from lack of efficacy. Withdrawal rates similar in observational studies vs RCTs. | See main results | Publication Bias Assessed:NRHeterogeneity Assessed:NRStandard Method of Study Appraisals:YesComprehensive Search Strategy:Yes Quality Rating: Fair |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Martinez Lopez et al., 2009219Country and setting:MultinationalFunding:Abbott ImmunologyAims of Review:To analyze the safety of MTX in RA regarding the reproductive system.Quality Rating:Fair | Study design:Systematic ReviewNumber of Patients:366Studies Included:N = 6 | Characteristics of Included Studies:RCTs, cohort studies, longitudinal observation studies and surveysCharacteristics of Included PopulationsRA patients who were 18 years or older; using MTX at doses usually taken in rheumatology (7.5-25 mg/w)Characteristics of Interventions:No true cohorts, only descriptions of cases obtained from retrospective clinical record searches or from surveys. The studies reported outcomes on male or female fertility; pregnancy complications; malformations, miscarriages, induced abortions, still births and breast feeding complications | Study Results:There were 101 MTX exposed pregnancies in the studies. The pooled outcomes (elective abortions not included) demonstrated: 19 miscarriages (23% of preganancies); 55 live births (66% of preganancies) and 5 of these had neonatal malformations (5% of pregnancies). The rate of induced abortions is 18%. No study filled the selection criteria for MTX and lactation or male fertility. However, there were case reports that generated possible indirect evidence of MTX in human breast milk and and reversible infertility. | Adverse Events:N/A |

| Study Characteristics | Study Design | ResultsAdverse Events  | Quality | Comments |
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| Author:Mertens, 2009220Country and setting:Multi-national (Europe, USA, Canada, Australia)Funding:Internal sources: * Minneapolis VA Medical Center
* NIH CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research)
* National Institute of Health

External sources: * No sources of support supplied
 | Study design:Systematic review and meta-analysisOverall study N:* N = 2872 (788 placebo, 2084 ANK) in systematic review
* Data not presented for 26 randomized pts (7 placebo, 19 ANK); therefore, N = 2846 (781 placebo, 2065 ANK) for analysis

Study aims:1. What is the clinical effectiveness of Anakinra for the treatment of RA in terms of: a. relieving symptoms?b. delaying disease progression?2. What are the risks (frequency and severity of adverse events) associated with Anakinra treatment in these patients? | Main results:Result 1. * ANK (< 50 mg/day ) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI)
* ACR 20: 1.38 (1.01, 1.89)
* ACR 50: 3.37 (0.82, 13.77)
* ACR 70: 4.45 (0.26, 76.62)
* Withdrawals: 0.85 (0.62, 1.18)
* Mean Difference (IV, Fixed, 95% CI)
* Change in pain VAS score: 0.85 (0.62, 1.18)
* Change in HAQ score: -0.2 (-0.33, -0.07)
* Change is ESR: -10.0 (-15.67, -4.33)(1 study)
* Change in CRP: -0.9 (-1.64, -0.16) (1 study)
* Change in Larsen score: -2.80 (-5.47, -0.13)

Result 2.* ANK (50 - 150 mg/day ) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI)
* ACR 20: 1.61 (1.32, 1.98)
* ACR 50: 2.51 (1.56, 4.03)
* ACR 70: 3.71 (1.44, 9.57)
* Withdrawals: 1.04 (0.86, 1.27)
* Mean Difference (IV, Fixed, 95% CI)
* Change in pain VAS score: -0.10 (-0.15, -0.04)
* Change in HAQ score: -0.19 (-0.30, -0.09)
* Change is ESR: -10.04 (12.75, -7.33)
* Change in CRP: -0.6 (-1.26, 0.06) (results from 1 study only)
* Change in Larsen score: -2.45 (-4.53, -0.36)

Adverse events:* ANK (50 - 150 mg/day ) vs.
* Placebo, Risk Ratio (M-H, Fixed, 95% CI)
* Infections: 1.08 (0.80, 1.45)
* Serious Infections: 3.15 (0.81, 12.20)
* Adverse Events: 1.05 (0.94, 1.17)
* Serious Adverse Events: 1.04 (0.70, 1.56)
* Injection site reactions: 2.45 (2.17, 2.77)
* Deaths: 1.01 (0.11, 9.04)
 | Review based on focused question of interest:YesDid search strategy employ comprehensive, systematic literature search?YesSearched Cochrane Central Register of Controlled Trials, MEDLINE (1950 to JanuaryWeek 4 2008), EMBASE (1980 to 2008), and CINAHL (1982 to November 2007); also reviewed reference lists of identified publications, including previous meta-analyses, to identify any additional studies/citations; further information was sought from authors/industry if needed.Eligibility criteria clearly described?YesReview studies independently reviewed by at least 2 persons?YesStandard method of critical appraisal before including?Yes | Comments:* Due to large variability in doses, 2 groups were created for analysis: data from doses < 50 mg/day of ANK and data from doses 50 to 150 mg/day. This was clinical decision based on fact that recommended daily dose is 100 mg daily.
* One of 5 included studies separted during analysis because of design differences (included another biologic).
* Pain VAS and radiographic scales and CRP were reported in just 1 of 5 studies.
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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Nam et al., 2010221Country and setting:MultinationalFunding:NRAims of Review:To review the evidence for the effi cacy and safety of biological agents in patients with rheumatoid arthritis (RA) to provide data to develop treatment recommendations by the European League Against Rheumatism (EULAR) Task ForceQuality Rating:Fair | Study design:Systematic review and meta-analysisNumber of Patients:NRStudies Included:87 articles and 40 abstracts | Characteristics of Included Studies:For efficacy 1)double-blind randomised controlled trials (RCTs); (2) trials of ≥6 months’ duration; (3) studies with ≥ 50 patients; (6) publications in English. And for safety (1) registries and observational studies; (2) inclusion of a control group; (3) report of incidence of events in the context of population-based expected incidencesCharacteristics of Included PopulationsPatients with RACharacteristics of Interventions:Studies evaluating 1 of the 9 biological DMARDs | Study Results:Efficacy - # of patients withdrawn for lack of efficacy* TNF inhibitors 5 studies n = 882 RR, 0.25 (95% CI, 0.13-0.48) *P* = 0.0001
* Sulfasalazine 5 studies n = 434 RR, 0.45 (95% CI, 0.23-0.89) *P* = 0.02
* Gold salts 2 studies n = 320 RR, 0.25 (95% CI, 0.11-0.53) *P* = 0.0003
* Leflunomide 1 study n = 190 RR, 0.44 (95% CI, 0.23-0.83) *P* = 0.01
* All DMARDs 12 studies n = 1081 RR, 0.39 (95% CI, 0.27-0.57) *P* = 0.00001
* All treatment 18 studies n = 2148 RR, 0.35 (95% CI, 0.25-0.49) *P* = 0.00001
 | Adverse Events:Toxicity - Withdrawals for adverse events* TNF inhibitors 5 studies n = 882 RR, 2.20 (95% CI, 0.82-5.91) *P* = 0.12 NNT/NNH, 0.25
* Sulfasalazine 5 studies n = 434 RR, 1.76 (95% CI, 0.98-3.14) *P* = 0.06 NNT/NNH, 0.93
* Gold salts 2 studies n = 320 RR, 2.34 (95% CI, 1.10-4.97) *P* = 0.03 NNT/NNH, 0.79
* Leflunomide 1 study n = 190 RR, 3.86 (95% CI, 1.20-12.39) *P* = 0.02 NNT/NNH, 0.45
* All DMARDs 12 studies n = 1081 RR, 2.32 (95% CI, 1.55-3.47) *P* = 0.0001 NNT/NNH, 0.86
* All treatment 18 studies n = 2148 RR, 2.33 (95% CI, 1.61-3.37) *P* = 0.00001 NNT/NNH, 0.62
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| **Study** **Characteristics**  | **Inclusion and Exclusion Criteria**  | **Characteristics and Interventions** | **Baseline Disease and Treatment Characteristics** | **Health Outcomes** |
| **Author, year, country, funding:**Osiri et al., 2002142Multinational Cochrane Collaboration**Study Design:**Systematic review of RCTs and CCTs**Aims of the Review:*** To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA
* META-ANALYSIS-analysis stratified comparison between LEF and Placebo or other DMARDs by outcomes at different length of txts

**Number of Pts:**1,144 LEF312 to Placebo680 to MTX132 to SSZOnly 920 used in meta-analysis-analysis 2 yr extension: LEF:158SSZ: 60MTX 101 | **Studies included:*** 6 trials

**Characteristics of included studies:*** Randomized, double-blind, placebo and/or active controlled

**Characteristics of included populations:*** All with active RA

**Characteristics of interventions:*** 5,10 or 25 mg/d vs. placebo or MTX or SSZ
 | LEF significantly better than placebo at 6,12 and 24 mos. * LEF vs. MTX
* ACR 20: Significantly more responders for MTX than LEF at 12 mos; OR: 1.43 (1.15-1.77)
* No significant differences at 2 yrs but more responders with MTX than with LEF; OR, 1.28 (0.98-1.67)
* ACR 50, ACR 70: differences in ACR 50/70 repsonses between LEF and MTX were NS
 | Total withdrawals lower in LEF group (10% greater than Placebo (70/416 vs. 18/311)); LEF not diff in efficacy and tolerability than MTX and SSZ, except that LEF was more efficaious than SSZ at 24 mos; AEs+ GI sympotms, elevated liver funcitn tests, alopecia, and infections | **Publication Bias Assessed**:NR**Heterogeneity Assessed:**Yes**Standard Method of Study Appraisals:**Yes**Comprehensive Search Strategy:**Yes **Quality Rating:** Good |

| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
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| Author, Year:Osiri et al., 2009222Country and setting:MultinationalFunding:Cochrane CollaborationAims of Review:To determine the efficacy and toxicity of LEF (monotherapy or combined with another DMARD) compared to placebo orother DMARDs in the treatment of RA.Quality Rating:Good | Study design:Systematic Review and meta-analysesNumber of Patients:NRStudies Included:N = 33 | Characteristics of Included Studies:All randomized controlled trials (RCTs) or controlled clinical trials(CCTs) comparing LEF as monotherapy or in combinationwith another DMARD to placebo or other DMARDs.Characteristics of Included PopulationsPatients were at least 18 yrs old, had a clinical diagnosis of RA according to the ACR 1987 revised criteria, and had active disease as shown by these outcomes:1) number of 10der joints;2) number of swollen joints;3) duration of morning stiffness;4) acute phase reactants.Characteristics of Interventions:Studies comparing LEF treatment (as monotherapy or incombination with other DMARDs) at a dose of 20 to 25 mg/day (with or without a loading daily dose of 100 mg given in the first1 to 3 days) with placebo or other DMARDs were included. The duration of treatment in the trials must have been at least 3 mos (or 12 wks). | Study Results:ACR20, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. MTX, at 3 mos: 0.96 (0.84-1.10)
* LEF vs. MTX, at 4 mos: 0.95 (0.50-1.81)
* LEF vs. MTX, at 6 mos (24 wks): 0.96 (0.87-1.06)
* LEF vs. MTX, at 12 mos: 1.08 (0.75-1.55)
* LEF vs. MTX, at 2 yrs: 1.05 (0.81-1.37)
* LEF vs. SSZ, at 6 mos: 1.03 (0.83-1.28)
* LEF vs. SSZ, at 12 mos: 1.03 (0.83-1.29)
* LEF vs. SSZ, at 24 mos: 0.73 (0.57-0.93)
* LEF+MTX vs.MTX, at 24 wks: 0.42 (0.29-0.63)
* LEF+SSZ vs. placebo+SSZ, at 24 wks: 0.96 (0.49-1.88)
* LEF vs. anti-TNF+MTX, at 24 wks: 1.14 (0.97-1.34)
* Lef+ADA vs. ADA, at 12 wks: 0.83 (0.69-0.99)

ACR50, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. MTX, at 12 mos: 0.86 (0.52-1.44)
* LEF vs. MTX, at 2 yrs: 0.82 (0.60-1.10)
* LEF vs. SSZ, at 6 mos: 0.92 (0.64-1.31)
* LEF vs. SSZ, at 12 mos: 0.93 (0.63-1.36)
* LEF vs. SSZ, at 24 mos: 0.48 (0.28-0.80)
* LEF+MTX vs.MTX, at 24 wks: 0.23 (0.11-0.48)
* LEF+SSZ vs. placebo+SSZ, at 24 wks: 0.10 (0.01-1.79)
* LEF vs. MTX, at 24 wks: 0.83 (0.53-1.32)
* LEF vs. anti-TNF+MTX, at 24 wks: 1.39 (0.97-1.99)
* Lef+ADA vs. ADA, at 12 wks: 0.84 (0.58-1.20)

ACR70, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. MTX, at 12 mos: 0.44 (0.26-0.77)
* LEF vs. MTX, at 2 yrs: 0.72 (0.44-1.18)
* LEF vs. SSZ, at 6 mos: 0.66 (0.28-1.55)
* LEF vs. SSZ, at 12 mos: 1.14 (0.57-2.25)
* LEF vs. SSZ, at 24 mos: 0.70 (0.34-1.43)
* LEF+MTX vs.MTX, at 24 wks: 0.23 (0.07-0.77)
* LEF vs. MTX, at 24 wks: 0.5 (0.10-2.53)
* LEF vs. anti-TNF+MTX, at 24 wks: 3.75 (1.35-10.43)

HAQ, Mean Difference (IV, Fixed, 95% CI)* LEF vs. MTX, at 3 mos: 0.01 (-0.12, 0.14)
* LEF vs. MTX, at 6 mos: -0.01 (-0.11-0.09)
* LEF vs. MTX, at 12 mos: -0.02 (-0.09-0.05)
* LEF vs. MTX, at 2 yrs: 0.05 (-0.04-0.14)
* LEF vs. SSZ, at 6 mos: -0.25 (-0.42- -0.08)
* LEF vs. SSZ, at 12 mos: -0.14 (-0.33-0.05)
* LEF vs. SSZ, at 24 mos, -0.29 (-0.57- -0.01)
* LEF+MTX vs. MTX, at 24 wks: -0.30 (-0.42- -0.18)
* LEF+SSZ vs. placebo+SSZ, at 24 mos: -0.07 (-0.20-0.06)
* LEF vs. anti-TNF, at 24 wks: 0.49 (0.34-0.64)

HAQ-DI, Mean Difference (IV, Fixed, 95% CI)* LEF+SSZ vs. placebo+SSZ, at 24 mos: -0.08 (-0.23-0.07)
* Lef/lLEF+ MTX vs. placebo/LEF + MTX, at 48 wks: 0.21 (0.05-0.37)

MHAQ, Mean Difference (IV, Fixed, 95% CI)* LEF vs. MTX, at 6 mos: -0.12 (-0.22- -0.02)
* LEF vs. MTX, at 12 mos: -0.14 (-0.25- -0.03)
* LEF vs. MTX, at 24 mos: -0.15 (-0.29- -0.01)
* LEF vs. MTX, at 4 mos: -2.34 (-7.64-2.96)

Chinese disability, Mean Difference (IV, Fixed, 95% CI)* LEF vs. MTX, at 3 mos: -0.09 (-0.18- -0.00)
* LEF vs. MTX, at 6 mos: -0.05 (-0.20-0.10)

SF-36, Mean Difference, Physical Component Scores (IV, Fixed, 95% CI) * LEF vs. MTX, at 12 mos: -3.0 (-5.41- -0.59)
* Lef/LEF + MTX vs.placebo/LEF + MTX, at 48 wks: -1.90 (5.14-1.34)

SF-36, Mean Difference, Mental Component Scores (IV, Fixed, 95% CI)* LEF vs. MTX, at 12 mos: -0.6 (-3.01-1.81)
* Lef/LEF + MTX vs.placebo/LEF + MTX, at 48 wks: -2.7 (5.63-0.23)

Work Productivity Scores, Mean Difference (IV, Fixed, 95% CI)* LEF vs. MTX, at 12 mos: -2.30 (-6.37-1.77)
* DAS28 response rate, Risk Ratio (M-H, Fixed, 95% CI)
* LEF + SSZ vs. SSZ, at 24 wks: 0.76 (0.47-1.24)

DAS28 score change, Mean Difference (IV, Fixed, 95% CI)* LEF + SSZ vs. SSZ, at 24 wks: 0.10 (-0.41-0.61)
* LEF vs. MTX, at 16 wks: 0.57 (0.24-0.90)
* LEF vs. MTX, at 24 wks: -0.10 (-0.41-0.21)
* LEF vs. anti-TNF+MTX, at 24 wks: 0.80 (0.43-1.17)
* DAS28 responders, Risk Ratio (M-H, Fixed, 95% CI)
* LEF + SSZ vs. SSZ, for 24-wk completers: 0.61 (0.36-1.04)

EULAR remission (DAS28 <3.2), Risk Ratio (M-H, Fixed, 95% CI)* LEF vs.MTX, at 16 wks: 1.24 (0.64-2.42)
* DAS28 remission, Risk Ratio (M-H, Fixed, 95% CI)
* LEF vs. MTX, at 24 wks: 1.0 (0.22-4.56)
* LEF vs. anti-TNF+MTX, at 24 wks: 1.67 (0.38-7.39)
* LEF vs. Lef+MTX, at 3 mos: 1.35 (0.18-10.09)

DAS28 low disease activity, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs. MTX, at 24 wks: 1.0 (0.28-3.63)
* LEF vs. anti-TNF+MTX, at 24 wks: 3.33 (1.17-9.51)

DAS28 moderate disease activity, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. MTX, at 24 wks: 1.05 (0.76-1.44)
* LEF vs. anti- TNF+MTX, at 24 wks: 0.56 (0.30-1.04)

DAS28 high disease activity, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. MTX, at 24 wks: 0.5 (0.05-5.22)
* LEF vs. anti-TNF+MTX, at 24 wks: 0.33 (0.02-6.44)

EULAR good response, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. LEF + MTX, at 3 mos: 0.37 (0.10-1.34)
* LEF + ADA vs. ADA, at 12 wks: 0.71 (0.47-1.05)

EULAR moderate response, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. Lef+MTX, at 3 mos: 0.80 (0.47-1.35)
* LEF + ADA vs. ADA, at 12 wks: 0.83 (0.73-0.93)
* EULAR response-no improvement, Risk Ratio (M-H, Fixed, 95% CI)
* LEF vs. LEF + MTX, at 3 mos: 4.27 (0.64-28.56)

EULAR response rate, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. MTX, at 16 wks: 1.05 (0.89-1.23)
 | Adverse Events:Total withdrawals, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs.SSZ, at 6 mos: 0.75 (0.53-1.07)
* LEF vs.SSZ, at 12 mos: 1.07 (0.43-2.63)
* LEF vs. SSZ, at 24 mos: 0.79 (0.39-1.59)
* LEF vs. MTX, at 12 mos: 1.26 (1.08-1.48)
* LEF vs. MTX, at 2 yrs: 1.15 (0.83-1.61)
* LEF + MTX vs. MTX, at
* 24 wks: 0.93 (0.60-1.43)
* LEF + SSZ vs. placebo + SSZ, at 24 wks: 1.34 (0.77-2.34)
* LEF/LEF+ MTX vs. placebo/Lef + MTX, at 48 wks: 1.4 (0.65-3.00)
* LEF + MTX vs. MTX, at 3
* mos: 0.75 (0.39-1.43)
* LEF+ MTX vs. MTX, at 24 mos: 1.25 (0.52,-3.01)

Withdrawals due to adverse events, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. SSZ, at 6 mos: 0.77 (0.45-1.33)
* LEF vs. SSZ, at 12 mos: 0.38 (0.08-1.90)
* LEF vs. SSZ, at 24 mos: 0.67 (0.25-1.76)
* LEF vs. MTX, at 6 mos: 0.24 (0.10-0.57)
* LEF vs. MTX, at 12 mos: 1.43 (1.13-1.83)
* LEF vs. MTX, at 2 yrs: 1.38 (0.77-2.47)
* LEF + MTX vs. MTX, at 24 wks: 1.82 (0.83-3.97)
* LEF/Lef + MTX vs. placebo/LEF + MTX, at 48 wks: 1.0 (0.21-4.83)
* LEF vs. LEF + MTX, at 3
* mos: 0.46 (0.03-8.03)
* LEF + MTX vs. MTX, at 3
* mos: 0.86 (0.41-1.81)
* LEF + MTX vs. MTX, at 24 mos: 1.4 (0.46-4.23)

Reported adverse events, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs. MTX, at 6 mos: 0.55 (0.42-0.73)
* LEF + MTX vs. MTX, at 24 mos: 3.5 (1.29-9.49)

Alopecia, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs. SSZ: 1.57 (0.63-3.93)
* LEF vs. MTX: 1.72 (1.32-2.24)
* LEF/Lef + MTX vs. placebo/LEF + MTX, at 48 wks: 8.0 (1.02-62.74)

GI symptoms, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. SSZ: 0.88 (0.63-1.22)
* LEF vs. MTX: 0.50 (0.28-0.92)

Allergy or rash, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs. SSZ: 1.0 (0.52-1.92)
* LEF vs. MTX: 1.51 (1.19-1.92)
* LEF + SSZ vs. placebo + SSZ, at 24 wks (rash): 1.12 (0.32-3.93)
* LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks (rash): 0.86 (0.30-2.46)

Nausea, Risk Ratio (M-H, Fixed, 95% CI)* LEF + SSZ vs. placebo + SSZ, at 24 wks: 3.57 (0.41-30.90)
* LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 1.33 (0.31-5.80)

Diarrhea, Risk Ratio (M-H, Fixed, 95% CI)* LEF + SSZ vs. placebo + SSZ, at 24 wks: 2.68 (0.29-24.93)
* LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 5.33 (1.61-17.71)

Hyper10sion, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs. SSZ: 1.0 (0.21-4.87)
* LEF vs. MTX: 2.29 (1.42-3.69)

W8 loss, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. SSZ: 3.0 (0.62-14.60)
* LEF vs. MTX: 0.81 (0.39-1.66)

Infections, Risk Ratio (M-H, Fixed, 95% CI) * LEF vs. SSZ: 0.25 (0.03-2.21)
* LEF vs. MTX: 0.97 (0.81-1.15)
* LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 2.5 (0.81-7.70)

Elevated liver function tests, Risk Ratio (M-H, Fixed, 95% CI)* LEF vs. SSZ: 0.6 (0.15-2.46)
* LEF vs. MTX: 0.66 (0.31-1.39)
* LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 1.07 (0.53-2.15)

Elevated liver function tests, reported as adverse event, Risk Ratio (M-H, Random, 95% CI)* LEF vs. SSZ, at 6 mos: 0.6 (0.15-2.46)
* LEF vs. MTX, at 6 mos: 0.52 (0.24-1.15)
* LEF vs. MTX, at 1 year: 0.65 (0.17-2.45)
* LEF vs. MTX, at 2 yrs: 0.80 (0.30-2.14)

Elevated liver function tests, withdrawals Risk Ratio (M-H, Random, 95% CI)* LEF vs. SSZ, at 6 mos: 1.0 (0.14-6.99)
* LEF vs. MTX, at 6 mos: 0.18 (0.02-1.63)
* LEF vs. MTX, at 1 year: 0.90 (0.28-2.86)
* LEF vs. MTX, at 2 yr: 0.33 (0.08-1.42)

Serious adverse events, (M-H, Fixed, 95% CI) * LEF + SSZ vs. placebo + SSZ, at 24 wks: 1.79 (0.47-6.77)
* LEF/Lef + MTX vs. placebo/Lef + MTX, at 48 wks: 0.87 (0.44,-1.72)
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| Study Characteristics  | Inclusion and Exclusion Criteria  | Characteristics and Interventions | Baseline Disease and Treatment Characteristics | Health Outcomes |
| Author, yr, country, funding:Rheumatoid Arthritis Clinical Trial Archive Group, 1995,223Multinational, NIH grantsStudy Design:Systematic reviewAims of the Review:To evaluate whether age and renal impairment affect rate of side effects or efficacy of MTX in RA ptsNumber of Pts:496 | Studies included:11 MTX clinical trials: * Weinblatt, et al., 1985
* Furst, et al., 1989
* Schmid, et al., unpublished study
* Williams, et al., 1985
* Wilke, et al., unpublished study
* Weinblatt, et al., 1990
* Williams, et al., 1992
* Suarez et al 1988
* Morassut, et al., 1989
* Hamdy, et al., 1987
* Bell, et al., 1988.

Characteristics of included studies:* RCTs
* Placebo control or comparative trial
* MTX as 1 treatment arm
* Adult RA pts
* Trial completed (although not necessarily published) by end of 1991, and trial 12 weeks or longer (to end or to crossover)

Characteristics of included populations:* Adult RA pts treated with MTX

Characteristics of interventions:* All pts treated with MTX (doses NR)
 | Study compares subgroups of pts treated with MTX* Neither age nor renal impairment had any effect on efficacy of MTX
* Odds of major clinical improvement by age were 1.0 for < 60 yr old group (referent), 1.4 (0.7, 2.6) for 60-64, 1.0 (0.5, 2.2) for 65-69, and 0.7 (0.3, 1.7) for ≥ 70 (efficacy regression analyses controlled for age group, sex, renal function, study of origin, initial tender joint count, grip strength, steroid dose, NSAID used at baseline, and maximum MTX dose)
* Odds of major clinical improvement by creatinine clearance were 1.0 for ≥99.8 ml/min (referent), 0.6 (0.3, 1.0) for 78.6-99.9 ml/min, 1.1 (0.6, 2.0) for 62.6-78.6 ml/min, and 1.0 (0.5, 2.1) for < 62.6 ml/min
* Age did not affect rate of toxicity. Those in the oldest group were not at a higher risk of side effects from MTX
 | No significant difference for liver toxicity between different creatinine clearance groups1.0 (referent)1.8 (1.0, 3.4)1.2 (0.6, 2.3)1.8 (0.8, 3.7)* Toxicity regressions adjusted for age, sex, creatinine clearance, baseline NSAID use (yes/no), maximum MTX dose, and study of origin
 | Publication Bias Assessed:NRHeterogeneity Assessed:YesStandard Method of Study Appraisals:NRComprehensive Search Strategy:Yes Quality Rating: Fair |

| Study Characteristics | Study Design | ResultsAdverse Events  | Quality | Comments |
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| Author:Salliot, 2009224Country and setting:NRFunding:NR | Study design:Systematic Review and meta-analysesOverall study N:N = 4,767 (745 rituximab, 1960 abatacept, 2062 anakinra), 2112 placeboStudy aims:To assess if biological agents, ie rituximab, abatacept, and anakinra increase risk of serious infections. | Main results:Pooled ORs Regardless of Dose:* Rituximab Pooled OR = 1.45 (0.56 - 3.73)
* Abatacept Pooled OR = 1.35 (0.78 - 2.32)
* Anakinra Pooled OR = 2.75 (0.90 - 8.35)

Pooled ORs Stratified by High and Low Dose:Rituximab* High Dose v Placebo 1.68 (0.64 - 4.35)
* Low Dose V Placebo 0.24 (0.01 - 4.33)
* High Dose v Low Dose 7.20 (0.43 - 120.66)

Abatacept * High Dose v Placebo 1.35 (0.78 - 2.33)
* Excluding patients receiving concominant treatment with other biologic DMARDs, pooled OR = 1.24 (0.70 - 2.29)
* Low Dose v Placebo 0.84 (0.13 - 5.30)
* High Dose v Low Dose 2.16 (0.52 - 8.98)
* Excluding patients receiving concominant treatment with other biologic DMARDs, pooled OR = 2.0 (0.48 - 8.33)

Anakinra* High Dose v Placebo 3.40 (1.11 - 10.46)
* Excluding patients with comorbidity factors, pooled OR = 1.67 (0.51 - 5.41)
* Low Dose v Placebo 0.51 (0.03 - 8.27)
* High Dose v Low Dose 9.63 (1.31 - 70.91)
* Excluding patients with comorbidity factors, pooled OR = 6.41 (0.81 - 50.30)

Adverse events:Rituximab:* Among 17 patients who had 1 serious infection: 5 had bronchopneumonia (1 presented with 2 episodes of Pseudomonas aeruginosa pneumonia), 2 septic arthritis (of whom one Staphylococcus aureus septicaemia), 3 pyelonephritis and 2 gastroenteritis and 1 each epiglottitis, cellulitis of a toe, and acute hepatitis B. One fatal bronchopneumonia occurred in a patient receiving rituximab.

Abatacept:* 49 serious infections occurring with abatacept were mainly bronchopulmonary, streptococcal and pyogenic septicaemia, staphylococcal arthritis, abscesses, gastrointestinal (6 of whom 3 diverticulitis), dermatological infections (6 of whom 1 was a cellulitis) and pyelonephritis. One case of unconfirmed tuberculosis and 1 case of pulmonary aspergillosis were reported. Last patient (who had history of tuberculosis and pulmonary fibrosis) died of aspergillosis and of Pseudomonas aeruginosa septicaemia.

Anakinra:* Among 30 serious infections occurring in anakinra-treated groups, 11 were pneumonia. Others were osteomyelitis, cellulitis, bursitis, herpes zoster, infected bunion and gangrene (1 of each). No related death or opportunistic infections were described.
 | Review based on focused question of interest:YesDid search strategy employ comprehensive, systematic literature search?Yes.A systematic literature search of literature published up to December 2007 was performed in PUBMED, EMBASE and Cochrane library databases; without limitation of years of publication or journal, using followings key-words: “rheumatoid arthritis,” “abatacept,’ “rituximab,” “anakinra,” “clinical controlled trials,” “clinical trials,” “randomised controlled trials,” “clinical trials phase II, III, IV”. We also included congress abstracts of American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) meetings from 2004 to 2006, because we assumed that any abstract published prior to 2004 had been published in a formal fulllength work. Moreover, to complete our search with unpublished data, Food and Drug Administration (FDA), European Agency for Evaluation of Medicinal Products (EMEA) and manufacturers (Roche, Amgen and Bristol- Myers Squibb) were contacted.Eligibility criteria clearly described?Yes.Inclusion criteria were randomised placebo controlled trials in adult patients with RA according to ACR criteria. Publications had to be written in English, French or Spanish. Patients had to be randomised to receive placebo or 1 of 3 biological agents (rituximab, anakinra and abatacept), as monotherapy or with concomitant biological or non-biological DMARDs. Reviews and articles reporting trials that were not placebo-controlled were excluded.Review studies independently reviewed by at least 2 persons?No. One reviewer selected studies and abstracted data.Standard method of critical appraisal before including?NR | Comments:NR |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Schipper et al., 2009225Country and setting:MultinationalFunding:NRAims of Review:To review the effects of the combination of MTX and SSZ in naïve patients and patients with an insufficient response, using the results of published parallel and add-on clinical trials in RA.Quality Rating:Fair | Study design:Systematic ReviewNumber of Patients:NRStudies Included:N = 4 | Characteristics of Included Studies:RCT of at least 12 weeks duration with a parallel or an add-on design,Characteristics of Included PopulationsRA patients fulfilling the ACR 1987 revised criteria; either naıve to MTX and SSZ (parallel trials) or had failed to 1 of them (add-on trials).Characteristics of Interventions:Placebo-controlled, double blind RCTs and compared the efficacy of combined MTX and SSZ to each individual agent and randomized open study comparing the combination of MTX and SSZ with MTX alone. | Study Results:Trials with naive patients:Mean DAS changes: sub-additive efficacy (1.3 and 1.9 respectively)ACR 20: 80%ACR50: 33%ACR70: 3% Trials with patients who failed SSZ: Mean DAS changes: additive efficacy. ACR 20: 29%ACR50: 11%ACR70: 4% | Adverse Events:From the 2 parallel trials, the first RCT showed more toxicity (nausea) of the MTX-SSZ combination compared with the single-drug arms. The second study showed more adverse events (nausea) in the combination group. The 2 add-on trials showed that the addition of MTX to SSZ in patients who had failed to the latter drug was clinically significantly superior to a switch to MTX alone, without increased toxicity. |

| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
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| Author, Year:Singh et al., 2009226Country and setting:MultinationalFunding:GovernmentAims of Review:To provide estimates of the benefits and safety of biologics in patients with RAQuality Rating:Good | Study design:Overview of SERs using ne2rk meta-analyses of Cochrane SERsNumber of Patients:NRStudies Included:6 SERs; 31 studies | Characteristics of Included Studies:In most of the included trials, each biologic was compared with a placebo, usually in combination with traditional DMARDs (usually MTX) or other biologicsCharacteristics of Included PopulationsEligibility criteria and patient populations weresimilar across reviews: adults with RA who met the ACR criteria for RACharacteristics of Interventions:ADA: All RCTs or CCTs comparing ADA (alone or combo with DMARDs) with placebo or other DMARDsABA: All RCTs comparing ABA (alone or combo with DMARDs) with placebo or other DMARDs; no restrictions on dosage or duration of the interventionANK: All RCTs comparing ANK (alone or combo with DMARDs or other biologics) with placebo or other DMARDs or biologicsETN: All RCTs or CCTs of at least 6 months’ duration comparing ETN with placebo, ETN with MTX, or ETN + MTX with MTX aloneINF: All RCTs comparing INF (1, 3, 5 or 10 mg/kg) + MTX with MTX alone, or INF with placebo, with a minimum duration of 6 months and at least 2 infusionsRIT: All RCTs comparing RIT (300, 350, 500 or 600 mg/m2) (alone or combo with DMARD) with placebo or other DMARDs or biologic | Study Results:Benefit (ACR 50), Biologic vs. Placebo, OR (95% CI), NNT* ABA: 2.98 (1.79-4.97), NNT, 4 (3-9)
* ADA: 3.70 (2.4-5.7), NNT, 4 (3-6)
* ANK: 1.68 (0.83-3.41), NNT, NS
* ETN: 4.97 (2.70-9.13), NNT, 3 (2-5)
* INF: 2.92 (1.37-6.24), NNT, 4 (2-18)
* RIT: 4.10 (2.02-8.33), NNT, 3 (1-7)
* Overall (all biologics vs. placebo): 3.35 (2.62-4.2)

Indirect comparison of ACR 50 between biologics, Ratio of odds ratios (95% CI)* ABA vs. ADA: 0.81 (0.43-1.49)
* ABA vs. ANK: 1.77 (0.78-4.00)
* ABA vs. ETN: 0.60 (0.29-1.25)
* ABA vs. INF: 1.02 (0.43-2.40)
* ABA vs. RIT: 0.73 (0.32-1.65)
* ADA vs. ANK: 2.20 (1.01-4.75)
* ADA vs. ETN: 0.74 (0.37-1.48)
* ADA vs. INF: 1.26 (0.56-2.86)
* ADA vs. RIT: 0.90 (0.41-1.96)
* ANK vs. ETN: 0.34 (0.14-0.81)
* ANK vs. INF: 0.58 (0.22-1.52)
* ANK vs. RIT: 0.41 (0.16-1.05)
* ETN vs. INF: 1.70 (0.68-4.22)
* ETN vs. RIT: 1.21 (0.51-2.90)
* INF vs. RIT: 0.71 (0.27-1.89)

ACR50 Subgroup data, OR (95% CI):Concomitant use of MTX Yes: 3.16 (2.40-4.16) No: 4.18 (2.48-7.06) Rheumatoid arthritis duration Early: 2.05 (1.24-3.38) Established: 3.47 (2.26-5.33) Late: 4.02 (2.89-5.59) Biologic is TNF-inhibitor Yes: 3.57 (2.57-4.97) No: 3.10 (2.12-4.53) Prior drugs failed Biologic: 4.09 (2.17-7.69) DMARD: 3.27 (2.46-4.35) None: 3.00 (1.11-8.13) Combination biologic therapy Yes: 1.00 (0.45-2.23) No: 3.60 (2.89-4.49) Duration of randomized trial Short: 4.03 (2.93-5.54) Intermediate: 2.92 (1.91-4.46) Long: 1.73 (0.78-3.82) Prior failure of TNF biologic Yes: 4.11 (2.21-7.63) No: 3.24 (2.48-4.22)  | Adverse Events:Safety (withdrawal due to an adverse event), OR (95% CI), NNT* ABA: 1.24 (0.88-1.76), NNT, NS
* ADA: 1.54 (1.12-2.12), NNT, 39 (19-162)
* ANK: 1.67 (1.22-2.29), NNT, 31 (17-92)
* ETN: 0.82 (0.56-1.19), NNT, NS
* INF: 2.21 (1.28-3.82), NNT, 18 (8-72)
* RIT: 1.34 (0.65-2.76), NNT, NS
* Overall: 1.39 (1.13-1.71)

Indirect comparison of withdrawal due to adverse events between biologics, Ratio of odds ratios (95% CI)* ABA vs. ADA: 0.80 (0.51-1.26)
* ABA vs. ANK: 0.74 (0.47-1.17)
* ABA vs. ETN: 1.52 (0.93-2.49)
* ABA vs. INF: 0.56 (0.30-1.05)
* ABA vs. RIT: 0.93 (0.43-2.02)
* ADA vs. ANK: 0.92 (0.60-1.42)
* ADA vs. ETN: 1.89 (1.18-3.04)
* ADA vs. INF: 0.70 (0.38-1.28)
* ADA vs. RIT: 1.15 (0.54-2.48)
* ANK vs. ETN: 2.05 (1.27-3.29)
* ANK vs. INF: 0.76 (0.41-1.39)
* ANK vs. RIT: 1.25 (0.58-2.69)
* ETN vs. INF: 0.37 (0.19-0.70)
* ETN vs. RIT: 0.61 (0.28-1.35)
* INF vs. RIT: 1.66 (0.69-3.98)

Withdrawal due to adverse event Subgroup data, OR (95% CI):Concomitant use of MTX Yes: 1.30 (1.02-1.65) No: 1.70 (1.12-2.57) Rheumatoid arthritis duration Early: 1.45 (0.92-2.28) Established: 1.25 (0.87-1.78) Late: 1.52 (1.09-2.11) Biologic is TNF-inhibitor Yes: 1.27 (0.94-1.69) No: 1.55 (1.14-2.11) Prior drugs failed Biologic: 1.74 (1.02-2.96) DMARD: 1.41 (1.11-1.79) None: 0.85 (0.41-1.76) Duration of randomized trial Short: 1.46 (1.07-1.99) Intermediate: 1.31 (0.94-1.82) Long; 1.47 (0.71-3.03) Prior failure of TNF biologic Yes: 1.76 (1.01-3.06) No: 1.34 (1.06-1.69)  |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Singh et al., 2009227Country and setting:NRFunding:Cochrane Collaboration; The Oak Foundation, Switzerland; NIH CTSA AwardAims of Review:To compare the efficacy and safety of ABA, ADA, ANK, ETN, INF, and RIT in RA ptsQuality Rating:Fair | Study design:Systematic ReviewNumber of Patients:NRStudies Included:N=6 (Note - 6 Cochrane reviews; data from 7 studies on ABA, 8 on ADA, 5 on ANK, 4 on ETN, 4 on INF, 4 on RIT) | Characteristics of Included Studies:Systematic reviews containing at least 1 RCT, with clinically relevant outcomes, and clear inclusion/exclusion criteria; completed, updated, and available Cochrane Systematic reviews of biologic DMARDs as of May 30, 2009Characteristics of Included Populations18 yo or older; RA according to 1987 ACR criteria (populations characteristics similar among reviews)Characteristics of Interventions:Biologic DMARDs along or in combo with other biologics/traditional DMARDs compared to placebo along or placebo + biologics/traditional DMARDs. Biologics were of the following dosing regimens: * ADA: 500 mg IV q 4 weeks for 2 weeks if <60 kg (750 mg if 60-100kg; 1000 mg if >100 kg)
* ADA: 40 mg SQ q 2 wks
* ANK: 100 mg SQ QD
* ETN: 25 mg SQ twice a wk
* INF: 3 mg/kg IV q 8 wks
* RIT: 2-1000 mg IV doses 2 wks apart
 | Study Results:ACR50 (OR, 95% CI, reference group is placebo) * ABA: 2.98 (1.79 to 4.97)
* ADA: 3.70 (2.40 to 5.70)
* ANK: 1.68 (0.83 to 3.41)
* ETN: 4.97 (2.70 to 9.13)
* INF: 2.92 (1.37 to 6.14)
* RIT: 4.10 (2.02 to 8.33)

Indirect comparions (only significant OR reported): * ANK less efficacy than ETN: 0.34 (0.14 to 0.81, *P* = 0.05)
* ADA greater efficacy than ANK: 2.20 (1.01 to 4.75, *P* = 0.046)
 | Adverse Events:Withdrawals due to ADEs (OR, 95% CI, reference group is placebo): * ABA: 1.24 (0.88-1.76)
* ADA: 1.54 (1.12-2.12)
* ANK: 1.67 (1.22-2.24)
* ETN: 0.82 (0.56-1.19)
* INF: 2.21 (1.28-3.82)
* RIT: 1.34 (0.65-2.76)

Indirect comparisons (only signficant OR reported): ADA more withdrawals due to ADEs than ETN: 1.89 (1.18 to 3.04; *P* = 0.009)ANK more withdrawals due to ADE than ETN: 2.05 (1.27 to 3.29; *P* = 0.003)ETN less withdrawals due to ADEs than INF: 0.39 (0.19 to 0.70; *P* = 0.002) |

| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
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| Author, Year:Singh et al., 2010228Country and setting:MultinationalFunding:NIHAims of Review:To compare the efficacy and safety of GOL in adults withrheumatoid arthritis.Quality Rating:Good | Study design:Systematic ReviewNumber of Patients:1714Studies Included:N = 4 | Characteristics of Included Studies:(RCTs) or Controlled Clinical Trials (CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation)Characteristics of Included PopulationsAdults 18 years or older, with RA meeting the 1987 American College of Rheumatology Classification criteria for RA. 1 study was prior mtx failure and biologic failure (smolen 99), 3 studies were naïve populationsCharacteristics of Interventions:Interventions compared are GOL alone or in combination with DMARDs or biologics vs.placebo plus MTX or GOL alone or in combination with DMARDs or biologics compared to other DMARDs or biologics. There were no restrictions with regard to dosage or duration of intervention. | Study Results:Compared to patients treated with placebo+MTX, patients treated with the FDA-approved dose of GOL+MTX (50 mg every 4 weeks) were 2.6 times more likely to reach ACR50 at 14-24 wks (95%confidence interval (CI) 1.3 to 4.9; *P* = 0.005 and NNT = 5, 95% CI, 2-20). GOL pts were 1.5 times more likely to reach ACR20 (CI) 1.3-4.9. GOL pts were 2.8 times more likely to reach ACR70 (CI) 1.3-5.98. GOL-treated patients were significantly more likely to achieve DAS remission (RR, 5.1 (CI) 1.7-15.7): Absolute risk difference = 10% (95% CI, 6%-14%). NNTB = 6 (95% CI, 2-35). GOL treated patients had a significantly greater change in DAS28 scores compared to placebo (*P*= 0.0003). GOL +MTX pts had greater improvement in functional ability (HAQ) and HAQ score decrease RR, 1.79 (CI) 1.38-2.31,*P*< 0.0001: Absolute risk difference, -20% (95% CI, -25%- -15%). Relative percent change, 11% (95% CI, -14% to-8.3%) NNT, 3 (95% CI, 3-4) compared to MTX + placebo (all statistically significant). | Adverse Events:Patients treated with the FDA-approved dose of GOL+MTX (50 mg every 4 weeks) no more likely to have any adverse event (relative risk 1.1, 95% Cl, 0.9-1.2; *P*= 0.44), and 0.5 times as likely to have overall withdrawals (95% Cl 0.3-0.8; *P*= 0.005). No significant differences were noted between GOL and placebo regarding serious adverse events, infections, serious infections *P*= 0.8, lung infections *P*= 0.9, tuberculosis *P*= 0.5, cancer *P*= 0.8, withdrawals due to adverse events *P*= 0.2 and inefficacy *P*= 0.1 and deaths *P*-0.99. No radiographic data were reported. GOL 100 mg every 4 weeks + MTX vs.placebo + ethotrexate: There was no significant difference between the number of adverse events and serious adverse events occurring for GOL treated patients compared to placebo treated patients with (*P*= 0.14) and (*P*= 0.9) respectively.There was no statistically significant difference between the number of infections between the GOL and placebo groups (*P*= 0.7).There was no statistically significant difference between the number of serious infections between the GOL and placebo groups (*P*= 0.3). There were no patients experiencing tuberculosis in either treatment or placebo groups. There was no statistically significant difference between the number of lung infections between the GOL and placebo groups (*P*= 0.1). There was no statistically significant difference between the GOL and placebo groups (*P*= 0.7) for cancer. Patients treated with GOL were 0.7 times less likely to withdraw compared to placebo.There was no statisticallysignificant difference between the number of patients withdrawing due to inefficacy in the placebo and treatment groups (*P*= 0.41), adverse eventss *P*= 0.24 or deaths *P*= 0.99. GOL 50 mg every 2 weeks + MTX vs.placebo + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events, infections, serious infections *P*= 0.97, cancer *P*= 0.5, withdrawals due to adverse events *P*= 0.97 and inefficacy *P*= 0.3. No deaths in either group. GOL 100 mg every 2 weeks + MTX vs.placebo + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events *P*= 0.7, infections, serious infections *P*= 0.5, withdrawals due to adverse events *P*= 0.3 and inefficacy *P*= 0.3. No deaths in either group. GOL 100 mg every 4 weeks + placebo (oral) vs.placebo (injections) + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events *P*= 0.7, infections *P*= 0.3, serious infections *P*= 0.7, withdrawals due to adverse events *P*= 0.4 and deaths *P*= 0.5. There were no inefficacy withdrawals. |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Singh et al., 2010229Country and setting:NRFunding:Cochrane Collaboration; NIH CTSA K12 AwardAims of Review:To assess the efficacy and safety of TCZ in RA ptsQuality Rating:Fair | Study design:Systematic ReviewNumber of Patients:3,334Studies Included:N = 8 | Characteristics of Included Studies:All multi-center trials; RCTs (or quasi-randomized trials)Characteristics of Included Populations18 yo or older (some studies 20 yo or older); 1987 ACR criteria for RA for 6 months or more; mean age in early 50sCharacteristics of Interventions:TCZ alone or in combination with DMARDs or biologics vs.placebo or other DMARDs or biologics; no restriction with dosage and duration of intervention; all patients on stable dose of MTX (10-25 mg a week) | Study Results:All results reported for 8 mg/kg TCZ +MTX vs. placebo +MTX. ACR50 (RR, 95% CI, TCZ vs. placebo): 3.17 (2.72 to 3.67); DAS remission (DAS<2.6): 8.74 (6.26 to 11.8); clinically significant HAQ decrease (HAQ improvement of >0.3 or MHAQ decease >0.22): 1.79 (1.62 to 1.94) | Adverse Events:TCZ 1.2 times more likely to have ADE vs.placebo (74% vs. 65%); serious ADEs: 1.17 (0.83 to 1.64); withdrawals due to ADEs: 1.43 (0.95 to 2.12) |

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| Study Characteristics  | Inclusion and Exclusion Criteria  | Characteristics and Interventions | Baseline Disease and Treatment Characteristics | Health Outcomes |
| Author, year, country, funding:Wailoo et al., 2006230AHRQStudy Design:Decision analytic model and meta-analysisanalysisAims of the Review:Cost effectiveness of ETN, ADA,, ANA and INF alone and in sequenceNumber of Patients:17,000 in disease registry (National Databank for Rheumatic Diseases) and 6694 in RCTs | Studies included:Disease registry (National Databank for Rheumatic Diseases) and 6694 in 13 RCTsCharacteristics of included studies:Treatment duration of at least 6 monthsCharacteristics of included populations:Adult patients with RACharacteristics of interventions:Placebo and MTX controlled | Odds ratio of ACR50* INF/ETN 1.17 (0.68, 2.08)
* ADA/ETN 1.02 (0.54, 1.97)
* ADA/INF 0.87 (0.47, 1.57)
 | NR | Publication Bias Assessed:YesHeterogeneity Assessed:NRStandard Method of Study Appraisals:NRComprehensive Search Strategy:Yes Quality Rating: Fair |

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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Wiens et al., 2009231Country and setting:NRFunding:NRAims of Review:To evaluate the efficacy and safety of ETN for treating RAQuality Rating:Fair | Study design:Systematic review and meta-analysisNumber of Patients:2385Studies Included:N = 8 | Characteristics of Included Studies:RCTsCharacteristics of Included Populations* Mean age: 47.5 to 54 yo
* Mean disease duration: 0.7 to 13 years
* Mean no. of previous DMARDs: 0.5 to 3.3
* Mean no. of swollen joints: 13.2 to 25
* Mean no. of 10der joints: 14 to 35
* % on steroids: 39 to 81
* Mean baseline HAQ score: 1.1 to 1.9

note: n ot all baseline characteristics reported in all studiesCharacteristics of Interventions:SQ doses of ETN compared to placebo group, with or without MTX. ETN dose was 25 mg twice a week or 50 mg weekly. | Study Results:ETN vs. control at 6 months* ACR20: 55% vs. 19%; RR, 2.94 (95% CI, 2.27-3.81)
* ACR50: 26% vs. 6%; RR, 5.28 (95% CI, 3.12-8.92)
* ACR70: 7% vs. 1%;RR, 4.83 (95% CI, 1.74-13.47)

ETN vs. control at 12 months* ACR20: 77% vs. 67%;RR, 1.14 (95% CI, 1.07-1.23)
* ACR50: 59% vs. 43%; RR, 1.36 (95% CI, 1.21-1.53)
* ACR70: 34% vs. 21%; RR, 1.56 (95% CI, 1.30-1.88)
 | Adverse Events:ETN vs. control* Serious AEs: RR, 0.88 (95% CI, 0.66-1.17; *P*=0.38)
* Serious infections: RR, 0.87 (95% CI, 0.60-1.26; *P*=0.57)
* Malignancy: RR, 1.48 (95% CI, 0.66-3.35); *P*=0.32)
* Deaths: RR, 1.51 (95% CI, 0.34-6.63; *P*=0.58)
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| Study Characteristics, Quality Rating | Study Information | Study Characteristics  | Results | Adverse Events |
| Author, Year:Wiens et al., 2010232Country and setting:MultinationalFunding:Brazilian National Council of Scientific and Technological Development.Aims of Review:To evaluate the efficacy and safety of using the anti-tumor necrosis factor- (anti-TNF- ) drugs ADA, ETN, and INF for the treatment of rheumatoid arthritis.Quality Rating:Fair | Study design:Systematic ReviewNumber of Patients:6503Studies Included:N = 21 | Characteristics of Included Studies:RCTsCharacteristics of Included PopulationsMean age 48-57, Disease duration 0.6 to 12 yrs, prior DMARDs 0-3, Treatment duration 12-2yrsCharacteristics of Interventions:Studies that compared the anti-TNF- drug with placebo, with or without concomitant MTX in both groups. From these RCTs, those that used the usual dosages for each of the anti-TNF- drugs—ADA 20 mg once/week or 40 mg every other week subcutaneously, ETN 25 mg twice/week or 50 mg once/week subcutaneously, and INF 3 mg/kg intravenously at weeks 0, 2, 6, and then every 8 weeks. | Study Results:With short-term treatment (12-30 wks), ETN demonstrated the highest risk ratios (RRs) for reaching ACR20 and ACR50. ADA demonstrated the highest RR, for achieving ACR70 ACR 20* ETN: 2.94, 95% CI: 2.27-3.81
* ADA: 2.26, 95% CI: 1.82-2.81
* INF 1.87, 95% CI: 1.43, 2.45

ACR 50* ETN: 5.28, 95% CI: 3.12-8.92
* ADA: 3.50, 95% CI: 2.75-4.44
* INF: 2.68, 95% CI: 1.79-3.99

ACR 70* ETN: 4.83, 95% CI: 1.74-13.47
* ADA: 5.36, 95% CI: 3.76-7.64
* INF: 2.68, 95% CI: 1.78-4.03

Over a long-term treatment course (1-3 yrs), ADA demonstrated the highest RRs (95% CIs) for these parameters: 1.85 (1.07-3.19), 2.80 (1.16-6.77), and 3.23 (1.37-7.61) for ACR20, ACR50, and ACR70, respectively. | Adverse Events:No statistically significant differences were noted in the safety of any of the 3 drugs compared with placebo (*P* > 0.05 for all parameters). INF had the highest RRs for withdrawing from the study due to lack of efficacy (2.05, 95% CI, 1.33-3.16) and adverse events (0.41, 95% CI, 0.18-0.95). |