Table 5. Strength of evidence for biologic DMARDs (KQ3)

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| **Outcome****Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Overall Tolerability: Withdrawals Total: Biologic DMARD vs. Placebo**41 RCT N = 18,029Studies included in mixed treatment comparison meta-analysis | MediumRCTs\* | Inconsistent | Indirect  | Precise  | Odds ratio of withdrawal overall: 0.51 (0.40-0.65) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol, etanercept, and rituximab had more favorable overall withdrawal profiles than most other biologic DMARDs | Low |
| **Overall Tolerability: Withdrawals due to Lack of Efficacy:****Biologic DMARD vs. Placebo**34 RCT N = 13,079Studies included in mixed treatment comparison meta-analysis | MediumRCTs\* | Consistent | Indirect  | Precise  | Odds ratio of withdrawal due to lack of efficacy: 0.21 (0.17-0.27) Indirect Comparisons:Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab and golimumab had fewer withdrawals than anakinra due to lack of efficacy. | Low |
| **Overall Tolerability: Withdrawals due to Adverse Events:****Biologic DMARD vs. Placebo**43 RCT N = 11,243Studies included in mixed treatment comparison meta-analysis | MediumRCTs\* | Consistent | Indirect  | Precise  | Odds ratio of withdrawal due to adverse events: 1.43 (1.18-1.74) Indirect Comparisons:No differences for most comparisons, except certolizumab pegol and infliximab had more withdrawals due to adverse events than abatacept, etanercept, and rituximab. Etanercept had fewer withdrawals due to adverse events than adalimumab, anakinra, or tocilizumab | Low |
| **Overall and Serious Adverse Events: Biologic DMARD vs. Biologic DMARD**1 RCT N = 4311 observational N = 2,364 | MediumRCT/fair; retrospective cohort/fair  | Consistent | Direct  | Precise  | Serious adverse events were more common with INF than with ABA, ADA, or ETN | Low |

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

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| **Outcome****Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Overall and Serious Adverse Events: Biologic DMARD vs. No Biologic DMARD**34 RCT N = 18,9796 observational N = 18,4766 meta-analysis N = 29,348 | LowRCT/31 fair; 3 good; observational/6 fair; meta-analysis/2 good, 4 fair | Inconsistent | Indirect  | Precise  | Mixed results; similar adverse event profiles among biologic DMARDs, with some studies indicating higher adverse event rates for biologic DMARDs given alone or in combination with oral DMARDs compared with placebo or no treatment. | Low |
| **Cardiovascular and Cerebrovascular Events :****Biologic DMARD vs. No Biologic DMARD**1 RCT N = 15011 observational N = 159,735 | HighRCT/1 fair; cohort, case-control, or other design/ 8 fair, 3 good | Inconsistent | Indirect  | Imprecise  | Mixed results; 1 cohort study found protective effect for heart failure, while 3 others found increased risk of heart failure with biologic DMARDs. 1 nested-case control study found no difference in risk for cardiovascular events, while 2 other studies found a protective effect with biologic DMARDs. 1 case-control study found no increased risk of stroke, and 2 cohort studies found no increased risk of MI. | Low |
| **Infections:****Biologic DMARD vs. Biologic DMARD**1 RCT N = 4312 observational N = 24,369 | MediumRCT/1 fair; Prospective cohort/2 fair | Inconsistent | Direct  | Imprecise  | Mixed results; 1 RCT reported more infections with INF than ABA (*P* = NR). 2 prospective cohort studies reported no differences in risk of serious infections comparing among ADA, ETA, and INF.  | Low |

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

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| **Outcome****Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Infections:****Biologic DMARD vs. No Biologic DMARD**6 RCT N = 5,014;26 observational N = 391,4036 meta-analysis | LowRCT/5 fair, 1 good; observational/ 20 fair, 6 goodmeta-analysis/5 fair, 1 good | Inconsistent | Indirect  | Precise  | Mixed results; most studies found either a trend towards increased infections or statistically significant increase in infections with biologic DMARDs. One meta-analysis reported a pooled odds ratio for serious infections of 2.0 (95% CI, 1.3-3.1) relative to placebo, another reported an increased risk of infection only with INF, and another found an increased risk of infection only with ANK | Moderate |
| **Infusion and Injection Site Reactions: Biologic DMARD vs. Biologic DMARD**1 RCT N = 4311 observational N = 14,0131 meta-analysis | MediumRCT/1 fair; prospective cohort/1 fair, meta-analysis/1 good | Consistent | Direct  | Precise  | Mixed results; 1 RCT reported more infusion reactions with INF than ABA (*P* = NR) and 1 retrospective cohort study reported more infusion reactions INF than with ADA and ETA. 1 meta-analysis found more reactions with ANK than ADA or ETA.  | Low |
| **Interstitial Lung Disease:** **Biologic DMARD vs. Biologic DMARD**1 observational N = 17,598 | Mediumprospective cohort/1 fair | Unknown | Direct  | Imprecise  | Current treatment with ETA and INF not associated with hospitalization for interstitial lung disease; Past treatment was for ETA (HR, 1.7; 95% CI, 1.0-3.0; *P* = 0.056) and INF (HR, 2.1; 95% CI, 1.1-3.8; *P* = 0.019) | Low |
| **Malignancies:****Biologic DMARD vs. Oral DMARD**6 observational N = 135,498 | MediumCohort/5 fair, 1 good | Inconsistent | Indirect  | Imprecise  | Mixed results; higher risk of lymphoma with biologic DMARDs in 1 study, but no difference in risk in another study. No increased risk of solid cancers or other malignancies for biologic DMARDs  | Low |

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

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| **Outcome****Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Malignancies:****Biologic DMARD vs. no Biologic DMARD**6 observational N = 70,3774 meta-analysis1 AERS data | MediumObservational/ 6 fair, meta-analysis/3 fair, 1 good | Unknown | Direct  | Imprecise  | Mixed results; some studies suggest small increased risk of malignancies including: lymphoma, nonmelanotic skin cancer, and melanoma | Low |

ABA, abatacept; ADA, adalimumab; ANK, anakinra; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; N, number; RA, rheumatoid arthritis; RCT, randomized controlled trial; vs., versus.

aThe dose of MTX used in this study is below the dose usually considered therapeutic. Thus this study does not provide evidence to determine how tocilizumab compares with MTC as it is generally used in clinical practice.