Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Oral DMARD vs. Oral DMARD: Corticosteroid vs. Corticosteroid**1 RCTN =143 | MediumRCT/fair | Unknown, single study | Direct  | Precise  | No difference in ACR 20 and DAS for prednisolone and budesonide | Low |
| **LEF vs. MTX**2 RCTs N = 1481 | LowRCTs/ FairLowRCTs/Fair | ConsistentConsistent | DirectIndirect | ImprecisePrecise | No difference in ACR 20 at 1 to 2 yearsNo difference in radiographic changes at 2 years | LowLow |
| **LEF vs. SSZ**1 RCTN =358 | MediumRCT/FairMediumRCT/Fair | Unknown, single studyUnknown, single study | DirectIndirect | ImpreciseImprecise | Mixed results for ACR20 response at 2 yrsSimilar Radiographic changes at 2 years  | InsufficientLow |
| **SSZ vs. MTX**3 RCTsN = 1001 | LowRCTs/FairLowRCTs/Fair | ConsistentConsistent | DirectIndirect | PreciseImprecise | No difference in disease activityNo difference in radiographic changes | LowLow |
| **Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticosteroids: SSZ + MTX vs. SSZ or MTX**3 RCTs, 1 Prospective cohort;N = 7092 RCTsN = 374 | Low1 RCT/FairLow2RCTs, 1 prospective cohort/FairLow2RCTs/Fair | Unknown, single studyConsistentConsistent | DirectDirectIndirect | ImprecisePrecisePrecise | Sulfasalazine + MTX improves disease activity (DAS), but no difference in ACR No differences in disease activity in patients with early RANo difference in radiographic changes | LowModerateLow |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **MTX + HCQ + SSZ vs. 1 or 2 oral DMARDs**2 RCTsN = 273 | LowRCTs/Good | Consistent | Direct | Imprecise | Improvement in disease activity in 3 versus 2 oral DMARDs | Moderate |
| **Oral DMARD + corticosteroid vs. Oral DMARD**2RCTsN = 717 | Low RCTs/fairLowRCT/ Fair | InconsistentConsistent | DirectIndirect | ImpreciseImprecise | Mixed results for disease activityLess radiographic changes with oral DMARD plus prednisone | InsufficientLow |
| **Biologic DMARDs vs. Biologic DMARDs**Mixed treatment comparison (MTC) 30 RCTsN = 6888\* | High MTC | Unknown, Single study | Indirect | Imprecise | No significant differences in disease activity (ACR 50 ) in MTC analyses for abatacept, adalimumab, golimumab,infliximab rituximab and tocilizumab in patients resistant to MTX | Low |
| **Biologic DMARDs vs. Biologic DMARDs: ABA vs. INF**1 RCT N = 431; (MTC) 30 RCTsN = 6888\* | Medium RCT/Fair, MTC | Inconsistent | Direct and Indirect | Imprecise | Abatacept improves disease activity over 1 year more than infliximabNo differences in ACR 50 in MTC analyses  | Low |
| **ADA vs ETN**1 prospective cohortN = 2326 | HighCohort/Fair | Unknown, single study | Direct | Imprecise | No difference in disease activity (ACR 70 respons) after 6 months | Low |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **ADA vs. INF**2 prospective cohortsN = 3033 Mixed treatment comparisons (MTC) 30 RCTsN = 6888\* | HighProspective cohorts/Fair, MTC | Consistent | Direct and Indirect | Imprecise | Adalimumab improves disease activity over 1 year more than infliximabNo differences in MTC analyses | Low |
| **ANA vs. Biologics** (MTC) 30 RCTsN = 6888\* | High, MTC | Unknown, single study | Indirect | Imprecise | Less improvement in disease activity (ACR 50) for anakinra compared to etanercept and anakinra. Comparisons with abatacept, golimumab, infliximab, rituximab and tocilizumab did not reach statistical significance. | Low |
| **ETN vs. Biologics** (MTC) 30 RCTs N = 6888\* | High, MTC | Unknown, single study | Indirect | Imprecise | In MTC analyses, greater improvement in disease activity (ACR 50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab, rituximab and tocilizumab. No significant differences when compared with golimumab. | Low |
| **ETN vs. INF**1 open label trial, 5 prospective cohortsN = 5883(MTC) 30 RCTs N = 6888\* | HighOpen label trial, prospective cohorts/Fair, MTC | Consistent | Direct and indirect  | Imprecise | Faster onset of efficacy for ETN but no differences at 1 year or laterMTC analyses (ACR 50: OR 4.17, 95% CI, 2.00-11.17) | Low |
| **RTX vs. anti TNF**1 prospective cohortN = 116 | HighProspective cohort/Fair | Unknown, single study | Direct | Precise | RTX reduces DAS 28 at 6 months more than anti-TNF | Low |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Biologic DMARDs vs. Oral DMARDs**4RCTs/2Cohorts N = 3696 | LowRCTs/ Cohorts/Fair | Consistent | Direct | Imprecise | Higher response rates for biologic DMARDs (ADA, ANA, ETN, INF, ) vs. oral DMARDs (MTX, LEF) in patients with inadequate response to prior DMARDs | Moderate |
| **Biologic DMARDs vs. Oral DMARDs: ADA vs. MTX**1 RCTN = 799 | LowRCT/FairLowRCT/Fair | Unknown, single studyUnknown, single study | DirectIndirect | PrecisePrecise | Lower response rates for ADA vs. MTX in early RALess radiographic progression for ADA vs. oral DMARD in early RA | LowLow |
| **ETN vs. Oral DMARDs**2RCTs, 1nonrandomized trialN =1687 | MediumRCT, nonrandomized trial/FairLow, RCTs/Fair | ConsistentConsstent | DirectIndirect | ImpreciseImprecise | Greater improvement in disease activity in ETN vs. oral DMARDLess radiographic progression for ETN vs. oral DMARD  | LowLow |
| **TCZ vs. MTX**1 RCTN = 127 | Low1 RCT/Fair | Unknown, single study | Direct | Precise | Great improvement in disease activity for Tocilizumab than MTX (8mg/wek) at 24wks | Insufficienta |
| **Biologic DMARDs + Biologic DMARDs vs. Biologic DMARDs: (1) ETN + AKA vs. ETN** **(2) ETN + ABA vs. ETN**2 RCTsN = 363 | Low2 RCTs/Fair | Consistent | Direct | Imprecise | No difference in disease activity | Low |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Any Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs**5 RCTs,4 cohorts; N = 98042 RCTsN = 1485 | LowRCTs/Fair, Cohorts/2 goodLow/Fair | ConsistentConsistent | DirectIndirect | ImpreciseImprecise | Improved disease activity with biologic plus MTXLess radiographic change with biologic plus MTX | ModerateLow |
| **Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs: ADA+ MTX vs. ADA**1 RCTN = 799 | Low1RCT/FairLow1RCT/Fair | Unknown, single studyUnknown, single study | DirectIndirect | PrecisePrecise | Higher ACR50 response for ADA + MTXLess radiographic change for ADA + MTX | LowLow |
| **ETN + DMARD vs. ETN**3 RCTs, 3 cohorts N = 8529  | MediumRCTs/Fair, cohorts /2Good,FairLow1RCT/Fair | ConsistentUnknown, single study | DirectIndirect | ImprecisePrecise | Trend toward improved disease activity for ETN+ MTX vs. ETNLess radiographic change for ETN + MTX vs. ETN | LowLow |
| **INF + MTX vs. MTX**1 Prospective cohortN = 2711 | MediumProspective cohort/Good | Unknown, single study | Direct | Precise | Improved disease activity for INF + MTX vs. INF | Low |
| **RTX +MTX vs. RTX**1 RCTN = 161 | LowRCT/Fair | Unknown, single study | Direct | Precise | Improved disease activity for RTX + MTX vs. RTX | Low |
| **Any Biologic DMARDs + Oral DMAR vs Oral DMARD**7 RCTsN = 4482 | LowRCTs/ 1 GoodLow3RCTs/1Good | ConsistentConsistent | DirectIndirect | PreciseImprecise | Greater improvement in disease activity for biologic + oral DMARDLess radiographic change for biologic + oral DMARD | HighModerate |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Biologic DMARDs + Oral DMARDs vs. Oral DMARDs: ABA + MTX vs. MTX**1 RCTN = 509 | LowRCT/GoodRCT/Good | Unknown,single studyUnknown, single study | DirectIndirect | PrecisePrecise | Greater improvement in disease activity (ACR50) for ABA + MTX vs MTXLess radiographic change for ABA + MTX | LowLow |
| **ADA + MTX vs. MTX**1 RCTN = 799 | Medium1 RCT/FairMediumRCT/Fair | Unknown, single studyUnknown, single study | DirectIndirect | PrecisePrecise | Improved disease activity for ADA + MTX vs. MTXLess radiographic change for ADA + MTX | LowLow |
| **ETN + oral DMARD vs. oral DMRD (MTX or SSZ)**3 RCTsN = 1488 | Low3RCTs/FairMedium1 RCT/Fair | Consist**e**ntUnknown, single study | DirectIndirect  | ImprecisePrecise | Improved disease activity for ETN + oral DMARD vs. oral DMARDLess radiographic change for ETN + MTX vs. MTX | ModerateLow |
| **GOL + MTX vs. MTX**1 RCTN = 637 | Medium1RCT/Fair | Unknown, single study | Direct | Precise | Improved disease activity (ACR50) for GOL + MTX vs. MTX | Low |
| **INF + MTX vs. MTX**1 RCTN = 1049 | Medium1 RCT/Fair | Unknown, single study | Direct | Precise | Improved disease activity for INF + MTX vs. MTX | Low |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs + Oral DMARDs: ANK + MTX vs. ANT + LEF; ETN + DMARD vs. INF + DMARD; Anti-TNF + MTX vs. anti-TNF vs. LEF**3 prospective cohortsN = 4225 | MediumProspective cohorts/Fair | Consistent | Direct | Imprecise | No significant difference between Biologic DMARD + Oral DMARD vs. Biologic DMARD + oral DMARD (ANK, INF, ETN, ADA with MTX or LEF) | Low |
| **Strategies in Early RA: Two oral DMARDs plus corticosteroid vs. oral DMARD**1 RCTN = 155 | Low 1RCT/GoodLow 1RCT/Good | Unknown, single studyUnknown, single study | DirectIndirect | PrecisePrecise | Improved disease activity in combination group at 28 weeks, but no difference by 52 weeksLess radiographic progression in combination group up to 5 years | LowLow |
| **Three oral DMARDs plus corticosteroid vs. oral DMARD**1 RCTN = 199 | MediumRCT/FairMediumRCT/Fair | Unknown, single studyUnknown, single study | DirectIndirect | PrecisePrecise | Higher remission in combination group at 2 years but not significant at 5 yrsLess radiographic progression in combination group up to 5 years | LowLow |
| **Three oral DMARDs vs. Biologic plus oral DMARD**1 RCT N = 258 | MediumRCT/Fair | Unknown, single study | Direct | Precise | Improved disease activity for Biologic DMARD plus oral DMARD compared to three oral DMARDs | Low |

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

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| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **(1)Sequential monotherapy vs. (2)Step-up combination therapy vs. (3)initial combination therapy with prednisone vs.(4) initial combination therapy with infliximab**1 RCTN = 508 | Low 1RCT/GoodLow 1RCT/Good | Unknown, single studyUnknown, single study | DirectIndirect | PrecisePrecise | No difference in remission by four years. Less radiographic progression in groups 3 and 4 by four years | LowLow |

ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; MTC, mixed treatment comparison; N, number; RA, rheumatoid arthritis rituximab, RIT; RCT, randomized controlled trial; sulfasalzine, SSZ; TCZ, tocilizumab; TNF, tumor necrosis factor; 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.