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 RCT  N =143 | Medium  RCT/  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 | Low  RCTs/ Fair  Low  RCTs/Fair | Consistent  Consistent | Direct  Indirect | Imprecise  Precise | No difference in ACR 20 at 1 to 2 years  No difference in radiographic changes at 2 years | Low  Low |
| **LEF vs. SSZ**  1 RCT  N =358 | Medium  RCT/Fair  Medium  RCT/Fair | Unknown, single study  Unknown, single study | Direct  Indirect | Imprecise  Imprecise | Mixed results for ACR20 response at 2 yrs  Similar Radiographic changes at 2 years | Insufficient  Low |
| **SSZ vs. MTX**  3 RCTs  N = 1001 | Low  RCTs/Fair  Low  RCTs/Fair | Consistent  Consistent | Direct  Indirect | Precise  Imprecise | No difference in disease activity  No difference in radiographic changes | Low  Low |
| **Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticosteroids: SSZ + MTX vs. SSZ or MTX**  3 RCTs, 1 Prospective cohort;  N = 709  2 RCTs  N = 374 | Low  1 RCT/Fair  Low  2RCTs, 1 prospective cohort/Fair  Low  2RCTs/Fair | Unknown, single study  Consistent  Consistent | Direct  Direct  Indirect | Imprecise  Precise  Precise | Sulfasalazine + MTX improves disease activity (DAS), but no difference in ACR  No differences in disease activity in patients with early RA  No difference in radiographic changes | Low  Moderate  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** |
| **MTX + HCQ + SSZ vs. 1 or 2 oral DMARDs**  2 RCTs  N = 273 | Low  RCTs/Good | Consistent | Direct | Imprecise | Improvement in disease activity in 3 versus 2 oral DMARDs | Moderate |
| **Oral DMARD + corticosteroid vs. Oral DMARD**  2RCTs  N = 717 | Low  RCTs/fair  Low  RCT/ Fair | Inconsistent  Consistent | Direct  Indirect | Imprecise  Imprecise | Mixed results for disease activity  Less radiographic changes with oral DMARD plus prednisone | Insufficient  Low |
| **Biologic DMARDs vs. Biologic DMARDs**  Mixed treatment comparison (MTC) 30 RCTs  N = 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 RCTs  N = 6888\* | Medium  RCT/Fair, MTC | Inconsistent | Direct and Indirect | Imprecise | Abatacept improves disease activity over 1 year more than infliximab  No differences in ACR 50 in MTC analyses | Low |
| **ADA vs ETN**  1 prospective cohort  N = 2326 | High  Cohort/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 cohorts  N = 3033  Mixed treatment comparisons (MTC)  30 RCTs  N = 6888\* | High  Prospective cohorts/Fair, MTC | Consistent | Direct and Indirect | Imprecise | Adalimumab improves disease activity over 1 year more than infliximab  No differences in MTC analyses | Low |
| **ANA vs. Biologics**  (MTC)  30 RCTs  N = 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 cohorts  N = 5883  (MTC) 30 RCTs  N = 6888\* | High  Open label trial, prospective cohorts/Fair, MTC | Consistent | Direct and indirect | Imprecise | Faster onset of efficacy for ETN but no differences at 1 year or later  MTC analyses (ACR 50: OR 4.17, 95% CI, 2.00-11.17) | Low |
| **RTX vs. anti TNF**  1 prospective cohort  N = 116 | High  Prospective 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 | Low  RCTs/ 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 RCT  N = 799 | Low  RCT/Fair  Low  RCT/Fair | Unknown, single study  Unknown, single study | Direct  Indirect | Precise  Precise | Lower response rates for ADA vs. MTX in early RA  Less radiographic progression for ADA vs. oral DMARD in early RA | Low  Low |
| **ETN vs. Oral DMARDs**  2RCTs, 1nonrandomized trial  N =1687 | Medium  RCT, nonrandomized trial/Fair  Low, RCTs/Fair | Consistent  Consstent | Direct  Indirect | Imprecise  Imprecise | Greater improvement in disease activity in ETN vs. oral DMARD  Less radiographic progression for ETN vs. oral DMARD | Low  Low |
| **TCZ vs. MTX**  1 RCT  N = 127 | Low  1 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 RCTs  N = 363 | Low  2 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 = 9804  2 RCTs  N = 1485 | Low  RCTs/Fair, Cohorts/2 good  Low/Fair | Consistent  Consistent | Direct  Indirect | Imprecise  Imprecise | Improved disease activity with biologic plus MTX  Less radiographic change with biologic plus MTX | Moderate  Low |
| **Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs: ADA+ MTX vs. ADA**  1 RCT  N = 799 | Low  1RCT/Fair  Low  1RCT/Fair | Unknown, single study  Unknown, single study | Direct  Indirect | Precise  Precise | Higher ACR50 response for ADA + MTX  Less radiographic change for ADA + MTX | Low  Low |
| **ETN + DMARD vs. ETN**  3 RCTs, 3 cohorts    N = 8529 | Medium  RCTs/Fair, cohorts /2Good,Fair  Low  1RCT/Fair | Consistent  Unknown, single study | Direct  Indirect | Imprecise  Precise | Trend toward improved disease activity for ETN+ MTX vs. ETN  Less radiographic change for ETN + MTX vs. ETN | Low  Low |
| **INF + MTX vs. MTX**  1 Prospective cohort  N = 2711 | Medium  Prospective cohort/Good | Unknown, single study | Direct | Precise | Improved disease activity for INF + MTX vs. INF | Low |
| **RTX +MTX vs. RTX**  1 RCT  N = 161 | Low  RCT/Fair | Unknown, single study | Direct | Precise | Improved disease activity for RTX + MTX vs. RTX | Low |
| **Any Biologic DMARDs + Oral DMAR vs Oral DMARD**  7 RCTs  N = 4482 | Low  RCTs/ 1 Good  Low  3RCTs/1Good | Consistent  Consistent | Direct  Indirect | Precise  Imprecise | Greater improvement in disease activity for biologic + oral DMARD  Less radiographic change for biologic + oral DMARD | High  Moderate |

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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 RCT  N = 509 | Low  RCT/Good  RCT/Good | Unknown,  single study  Unknown, single study | Direct  Indirect | Precise  Precise | Greater improvement in disease activity (ACR50) for ABA + MTX vs MTX  Less radiographic change for ABA + MTX | Low  Low |
| **ADA + MTX vs. MTX**  1 RCT  N = 799 | Medium  1 RCT/Fair  Medium  RCT/Fair | Unknown, single study  Unknown, single study | Direct  Indirect | Precise  Precise | Improved disease activity for ADA + MTX vs. MTX  Less radiographic change for ADA + MTX | Low  Low |
| **ETN + oral DMARD vs. oral DMRD (MTX or SSZ)**  3 RCTs  N = 1488 | Low  3RCTs/Fair  Medium  1 RCT/Fair | Consist**e**nt  Unknown, single study | Direct  Indirect | Imprecise  Precise | Improved disease activity for ETN + oral DMARD vs. oral DMARD  Less radiographic change for ETN + MTX vs. MTX | Moderate  Low |
| **GOL + MTX vs. MTX**  1 RCT  N = 637 | Medium  1RCT/Fair | Unknown, single study | Direct | Precise | Improved disease activity (ACR50) for GOL + MTX vs. MTX | Low |
| **INF + MTX vs. MTX**  1 RCT  N = 1049 | Medium  1 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)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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 cohorts  N = 4225 | Medium  Prospective 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 RCT  N = 155 | Low  1RCT/Good  Low  1RCT/Good | Unknown, single study  Unknown, single study | Direct  Indirect | Precise  Precise | Improved disease activity in combination group at 28 weeks, but no difference by 52 weeks  Less radiographic progression in combination group up to 5 years | Low  Low |
| **Three oral DMARDs plus corticosteroid vs. oral DMARD**  1 RCT  N = 199 | Medium  RCT/Fair  Medium  RCT/Fair | Unknown, single study  Unknown, single study | Direct  Indirect | Precise  Precise | Higher remission in combination group at 2 years but not significant at 5 yrs  Less radiographic progression in combination group up to 5 years | Low  Low |
| **Three oral DMARDs vs. Biologic plus oral DMARD**  1 RCT    N = 258 | Medium  RCT/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)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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 RCT  N = 508 | Low  1RCT/Good  Low  1RCT/Good | Unknown, single study  Unknown, single study | Direct  Indirect | Precise  Precise | No difference in remission by four years.  Less radiographic progression in groups 3 and 4 by four years | Low  Low |

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.