Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2)

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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 | MediumRCT/fair | Unknown, single study | Direct  | Precise  | Greater improvement in functional capacity and quality of life with prednisolone than with budesonide | Low |
| **Leflunomide vs. MTX**2 RCTsN = 1481  | LowRCTs/ 2 fairMediumRCT/1 fair | InconsistentUnknown, single study | DirectDirect | Imprecise\*Precise | No clinically significant difference for change in functional capacity. Although some results reached statistically significant differences favoring leflunomide (mean improvement in HAQ-DI: -0.45 vs. -0.26, *P* ≤ 0.01), neither study reported a difference reaching the MCID.Greater improvement in quality of life (SF-36 physical summary score, but not mental summary score) with LEF than MTX | LowLow |
| **Leflunomide vs. Sulfasalazine**1 RCTN = 358 | MediumRCT/fair | Unknown, single study | Direct | Precise | Greater improvement in functional capacity with LEF than SSZ  | Low |
| **Sulfasalazine vs. MTX**3 RCTsN = 479 | LowRCTs/Fair | Consistent | Direct | Precise | No difference in functional capacity | Moderate |

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticoster-oids: SSZ + MTX vs. SSZ or MTX monotherapy**3 RCTsN = 479 | LowRCTs/Fair | Consistent | Direct | Precise | No difference in functional capacity | Moderate |
| **Oral DMARD + corticosteroid vs. Oral DMARD**2 RCTsN = 7171 RCTN = 467 | LowRCTs/ Good, FairLowRCT/Good | ConsistentUnknown, single study | DirectDirect | ImpreciseImprecise | Greater improvement in functional capacity for subjects treated with oral DMARD plus prednisoloneNo difference in quality of life | ModerateLow |
| **Biologic DMARD vs. Biologic DMARD: ABA vs. INF**1 RCTN = 431 | MediumRCT/Fair | Unknown, single study | Direct | ImpreciseImprecise | No difference in functional capacityStatistically significant difference between groups for quality of life (SF-36 PCS but not MCS) that did not reach the MCID. | LowLow |
| **ETN vs. INF**3 prospective cohort studies;N = 2239 | MediumProspective cohorts/3 FairMedium to HighProspective cohort/1 Fair | InconsistentUnknown, single study | DirectDirect | ImprecisePrecise | Mixed results for functional capacity (2 of 3 studies reported no difference; 1 favored ETN)Reported statistically significantly greater improvement in quality of life with ETN (*P* = 0.001), but data NR (in Figure only) and CIs appear to overlap in the Figure  | InsufficientInsufficient |
| **ADA vs. ETN**1 prospective cohort N = 707 | Medium to HighProspective cohort/Fair | Unknown, single study | Direct | Imprecise | No difference in functional capacityNo difference in quality of life  | Low |

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **ADA vs. INF**1 prospective cohort;N = 707 | Medium to HighProspective cohort/Fair | Unknown, single study | Direct | Precise | Statistically significant difference between groups favoring ADA for improvement in functional capacity that did not reach the MCID (mean change in HAQ: -0.42 vs. -0.26, *P* < 0.05)Reported statistically significantly greater improvement in quality of life with ADA (*P* = 0.001), but data NR (in Figure only) and CIs appear to overlap in the Figure | LowInsufficient |
| **Biologic DMARD vs. Oral DMARD: ADA vs. MTX**1 RCTN = 799 | MediumRCT/Fair | Unknown, single study  | Direct | Precise | No difference in functional capacity for MTX naïve subjects with early RA | Low |
| **ETN vs. MTX**2 RCTsN =13181 RCTN = 632 | LowRCTs/1 Good, 1 FairMediumRCT/1 Fair | InconsistentUnknown, single study | DirectDirect | ImpreciseImprecise | Mixed results for functional capacityFaster improvement in quality of life with ETN (greater improvement at 12 weeks, but no difference from weeks 16 to 52) | InsufficientLow |
| **TCZ vs. MTX**1 RCTN = 127 | MediumRCT/Fair | Unknown, single study | Direct | Precise | Greater improvement in functional capacity with TCZ than MTX (8mg/week) for patients with active RA and an inadequate response to MTX | Insufficienta |
| **Biologic DMARD + Biologic DMARD vs. Biologic DMARD: ETN + ABA vs. ETN**1 RCTs N = 121 | MediumRCT/Fair | Unknown, single study | Direct | Imprecise | No difference functional capacityGreater improvement in physical, but not mental, health-related quality of life | Low |

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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 DMARDsb**2 RCTsN = 1495 | LowRCTs/1 Good, 1 FairLowRCT/1 Good | ConsistentUnknown, single study | DirectDirect | ImprecisePrecise | Greater improvement in functional capacity with biologic + MTXGreater improvement in quality of life with biologic + MTX | ModerateLow |
| **Biologic DMARD + MTX vs. Biologic DMARD in MTX naïve subjects or those not recently on MTXb: ADA+ MTX vs. ADA**1 RCTN = 799 | MediumRCT/Fair | Unknown, single study | Direct | Precise | Greater improvement in functional capacity with ADA + MTX for MTX-naïve subjects with early RA. | Low |
| **ETN + MTX vs. ETN**1 RCTs, 1 cohort studyN = 696  | LowRCT/ Good | Unknown, single study | Direct | Precise | Greater improvement in functional capacity and quality of life with ETN + MTX for subjects with active RA who failed at least 2 oral DMARDs, but were not on MTX for at least 6 months. | Low |
| **Biologic DMARD + Oral DMARD vs. Biologic DMARD in subjects with active RA despite treatment with the same Oral DMARDb : ETN + DMARD vs. ETN**2 RCTs, 1 cohort studyN = 3609  | LowRCTs/2 FairCohort/Fair | Consistent | Direct | Precise | No difference in functional capacity No difference in quality of life | Moderate |

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Any Biologic DMARDs + Oral DMARD vs. Oral DMARD**7 RCTs, 1 cohort studyN = 7516 | LowRCTs/ 5 Fair, 2 GoodCohort/FairLowRCTs/3 Fair, 1 Good | ConsistentConsistent | DirectDirect | PrecisePrecise | Greater improvement in functional capacity with biologic + oral DMARDGreater improvement in quality of life with biologic + oral DMARD | HighModerate |
| **Biologic DMARD + Oral DMARD vs. Oral DMARD: ABA + MTX vs. MTX**1 RCT N = 509 | LowRCT/Good | Unknown, single study | Direct | Imprecise | Statistically significant differences for improvement in functional capacity and quality of life (SF-36 PCS) with ABA + MTX, but differences did not reach MCIDs | Low |
| **ADA + MTX vs. MTX**1 RCTN = 799 | MediumRCT/Fair | Unknown, single study | Direct | Precise | Greater improvement in functional capacity with ADA + MTX | Low |
| **ETN + oral DMARD vs. oral DMARD (MTX or SSZ)**3 RCTs, 1 cohort studyN = 4522 | LowRCTs/2 Fair, 1 GoodCohort/FairLowRCTs/ 1 Fair, 1 Good | ConsistentConsistent | DirectDirect | PrecisePrecise | Greater improvement in functional capacity with ETN + oral DMARDGreater improvement in quality of life with ETN + oral DMARD | ModerateModerate |
| **GOL + MTX vs. MTX**1 RCT N = 637 | MediumRCT/Fair | Unknown, single study | Direct | Imprecise | Greater numerical improvement in functional capacity with GOL 50 + MTX compared with MTX, but difference was not statistically significantly (Median % improvement in HAQ-DI: 43.65 vs. 36.95, *P* = 0.141) | Low |
| **INF + MTX vs. MTX**1 RCTN = 1049 | MediumRCT/Fair | Unknown, single study | Direct | Precise | Greater improvement in functional capacity and quality of life with INF + MTX | Low |

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug Comparison****Number of Studies** **# of Subjects** | **Risk of Bias****Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Biologic DMARD + Oral DMARD vs. Biologic DMARD + Oral DMARD: Anti-TNF + MTX vs. anti-TNF + LEF**1 cohortN = 1218 | MediumCohort/Fair | Unknown, single study | Direct | Imprecise | No difference in functional capacity  | Low |
| **Strategies in Early RA: Two oral DMARDs plus corticosteroid vs. oral DMARD**1 RCTN = 155 | Low RCT/Good | Unknown, single study | Direct | Precise | More rapid improvement in functional capacity (comparing groups at 28 weeks), but no difference by 56 weeks | Low |
| **Three oral DMARDs plus corticosteroid vs. oral DMARD**1 RCTN = 199 | MediumRCT/Fair | Unknown, single study | Direct | Precise | Less work disability in the combination strategy group | Low |
| **Other combination strategies: Sequential monotherapy vs. Step-up combination therapy vs. initial combination therapy with prednisone vs. initial combination therapy with infliximab**1 RCTN = 508 | Low RCT/Good | Unknown, single study | Direct | Precise | More rapid improvement in functional capacity in groups 3 and 4 than in groups 1 and 2(statistically significantly better at 3, 6, 9, and 12 months). By two years, improvement was maintained in all groups, but there were no statistically significant differences between groupsSimilar pattern was found for improvement in physical health-related quality of life | Low |

ABA, abatacept; ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; MCID, minimal clinically important difference; MTX, methotrexate; N, number; RCT, randomized controlled trial; TCZ, tocilizumab; vs., versus.

\*This was considered imprecise based on the high degree of uncertainty around the effect size, partly due to one of the studies not reporting any quantitative information.

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 MTX as it is generally used in clinical practice.

bFor Biologic DMARD + Oral DMARD vs. Biologic DMARD, we stratified by population because results differed based on the population enrolled