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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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 | Greater improvement in functional capacity and quality of life with prednisolone than with budesonide | Low |
| **Leflunomide vs. MTX**  2 RCTs  N = 1481 | Low  RCTs/ 2 fair  Medium  RCT/1 fair | Inconsistent  Unknown, single study | Direct  Direct | 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 | Low  Low |
| **Leflunomide vs. Sulfasalazine**  1 RCT  N = 358 | Medium  RCT/fair | Unknown, single study | Direct | Precise | Greater improvement in functional capacity with LEF than SSZ | Low |
| **Sulfasalazine vs. MTX**  3 RCTs  N = 479 | Low  RCTs/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 RCTs  N = 479 | Low  RCTs/Fair | Consistent | Direct | Precise | No difference in functional capacity | Moderate |
| **Oral DMARD + corticosteroid vs. Oral DMARD**  2 RCTs  N = 717  1 RCT  N = 467 | Low  RCTs/ Good, Fair  Low  RCT/Good | Consistent  Unknown, single study | Direct  Direct | Imprecise  Imprecise | Greater improvement in functional capacity for subjects treated with oral DMARD plus prednisolone  No difference in quality of life | Moderate  Low |
| **Biologic DMARD vs. Biologic DMARD: ABA vs. INF**  1 RCT  N = 431 | Medium  RCT/Fair | Unknown, single study | Direct | Imprecise  Imprecise | No difference in functional capacity  Statistically significant difference between groups for quality of life (SF-36 PCS but not MCS) that did not reach the MCID. | Low  Low |
| **ETN vs. INF**  3 prospective cohort studies;  N = 2239 | Medium  Prospective cohorts/3 Fair  Medium to High  Prospective cohort/1 Fair | Inconsistent  Unknown, single study | Direct  Direct | Imprecise  Precise | 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 | Insufficient  Insufficient |
| **ADA vs. ETN**  1 prospective cohort  N = 707 | Medium to High  Prospective cohort/Fair | Unknown, single study | Direct | Imprecise | No difference in functional capacity  No 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 High  Prospective 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 | Low  Insufficient | |
| **Biologic DMARD vs. Oral DMARD: ADA vs. MTX**  1 RCT  N = 799 | Medium  RCT/Fair | Unknown, single study | Direct | | Precise | No difference in functional capacity for MTX naïve subjects with early RA | | Low |
| **ETN vs. MTX**  2 RCTs  N =1318  1 RCT  N = 632 | Low  RCTs/1 Good, 1 Fair  Medium  RCT/1 Fair | Inconsistent  Unknown, single study | Direct  Direct | | Imprecise  Imprecise | Mixed results for functional capacity  Faster improvement in quality of life with ETN (greater improvement at 12 weeks, but no difference from weeks 16 to 52) | | Insufficient  Low |
| **TCZ vs. MTX**  1 RCT  N = 127 | Medium  RCT/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 | Medium  RCT/Fair | Unknown, single study | Direct | | Imprecise | No difference functional capacity  Greater 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 RCTs  N = 1495 | Low  RCTs/1 Good, 1 Fair  Low  RCT/1 Good | Consistent  Unknown, single study | Direct  Direct | | Imprecise  Precise | Greater improvement in functional capacity with biologic + MTX  Greater improvement in quality of life with biologic + MTX | Moderate  Low |
| **Biologic DMARD + MTX vs. Biologic DMARD in MTX naïve subjects or those not recently on MTXb: ADA+ MTX vs. ADA**  1 RCT  N = 799 | Medium  RCT/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 study  N = 696 | Low  RCT/ 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 study  N = 3609 | Low  RCTs/2 Fair  Cohort/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 study  N = 7516 | Low  RCTs/ 5 Fair, 2 Good  Cohort/Fair  Low  RCTs/3 Fair, 1 Good | Consistent  Consistent | Direct  Direct | | Precise  Precise | Greater improvement in functional capacity with biologic + oral DMARD  Greater improvement in quality of life with biologic + oral DMARD | | High  Moderate |
| **Biologic DMARD + Oral DMARD vs. Oral DMARD: ABA + MTX vs. MTX**  1 RCT  N = 509 | Low  RCT/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 RCT  N = 799 | Medium  RCT/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 study  N = 4522 | Low  RCTs/2 Fair, 1 Good  Cohort/Fair  Low  RCTs/ 1 Fair, 1 Good | Consistent  Consistent | Direct  Direct | | Precise  Precise | Greater improvement in functional capacity with ETN + oral DMARD  Greater improvement in quality of life with ETN + oral DMARD | | Moderate  Moderate |
| **GOL + MTX vs. MTX**  1 RCT  N = 637 | Medium  RCT/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 RCT  N = 1049 | Medium  RCT/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 cohort  N = 1218 | Medium  Cohort/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 RCT  N = 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 RCT  N = 199 | Medium  RCT/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 RCT  N = 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 groups  Similar 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