Table 4. Strength of evidence for oral DMARDs (KQ3)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome**  **Drug Comparison**  **Number of Studies**  **# of Subjects** | **Risk of Bias**  **Design/ Quality** | **Consistency** | **Directness** | **Precision** | **Results** | **Strength of Evidence** |
| **Overall Tolerability:**  **Oral DMARD vs. Oral DMARD**  3 RCT  N = 1839  1 observational  N = 40,594;  3 meta-analysis  N = 7,245 | Low  RCTs/3 fair  Retrospective cohort/1 fair  meta-analysis/2 good, 1 fair | Inconsistent | Direct | Precise | Similar tolerability and discontinuation rates for HCQ, LEF, MTX, and SSZ, with the exception of one study noting better tolerability for LEF and one study noting better tolerability with MTX | Low |
| **Overall Tolerability:**  **Oral DMARD vs. Oral or Biologic DMARD combination**  6 RCTs  N = 841  2 observational  N = 349  2 meta-analysis  N = 1,735 | Low  RCTs/2 good, 4 fair  cohort/2 fair  meta-analysis/1 good, 1 fair | Inconsistent | Direct | Precise | Similar withdrawal rates due to adverse events with exception of one study showing increased withdrawal for SSZ + MTX combination; DMARD combination may have more adverse events | Moderate |
| **Overall Tolerability:**  **Oral DMARD + Corticosteroid vs. Oral DMARD**  4 RCT  N = 1202  1 observational  N = 154 | Low  RCTs/1 good, 3 fair  retrospective cohort/1fair | Consistent | Direct | Precise | Similar tolerability and rates of serious adverse events; addition of corticosteroid to oral DMARD lowered withdrawal due to adverse events | Moderate |

Table 4. Strength of evidence for oral DMARDs (KQ3)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome**  **Drug Comparison**  **Number of Studies**  **# of Subjects** | | **Risk of Bias**  **Design/ Quality** | | | | **Consistency** | | | **Directness** | | **Precision** | | | **Results** | | | **Strength of Evidence** | |
| **Cardiovascular and Cerebrovascular Events:**  **Oral DMARD vs. Oral DMARD vs. Oral DMARD combination**  4 observational  N = 119,929 | Medium  observational/ 4 fair | | | | Consistent | | | Indirect | | Imprecise | | | Oral DMARDs and combinations of oral DMARDS may reduce cardiovascular risk; risk reductions were larger in magnitude with LEF | | | Low | |
| **Hepatic Events:**  **Oral DMARD vs. Oral DMARD vs. Biologic DMARD**  2 observational  N = 82,479 | Medium  observational/ 2 fair | | | | Consistent | | | Indirect | | Imprecise | | | Similar hepatic event rates for LEF, MTX, and other oral DMARDs | | | Low | |
| **Infection:**  **Oral DMARD vs. Oral DMARD**  6 observational  N = 142,522 | Medium  observational/ 4 fair, 2 good | | | | Inconsistent | | | Direct | | Imprecise | | | Mixed results; inconsistent differences for infection rates for comparisons of HCQ, LEF, MTX, and SSZ | | | Low | |
| **Oral DMARD vs. no Oral DMARD**  6 observational  N = 236,151 | Medium  observational/ 6 fair | | | | Inconsistent | | | Indirect | | Imprecise | | | Mixed results; increased risk of infection in some studies, while other show decreased infection risk | | | Insufficient | |
| **Interstitial Lung Disease:**  **Oral DMARD vs. Oral DMARD**  2 observational  N = 80,332 | | | Medium  observational/ 2 fair | Inconsistent | | | Direct | | | | Imprecise | Mixed results; increased risk with LEF in one study, while another study found no differences among HCQ, LEF, MTX, and SSZ | | | Insufficient | | | |
| **Malignancy:**  **Oral DMARD vs. Oral DMARD vs. corticosteroid**  2 observational  N = 16,545 | | | Medium  observational/ 1 good, 1 fair | Consistent | | | Direct | | | | Imprecise | No differences in lymphoma for MTX and SSZ, and no difference in non-melanoma skin cancer for LEF and MTX | | | Low | | | |

Table 4. Strength of evidence for oral DMARDs (KQ3)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome**  **Drug Comparison**  **Number of Studies**  **# of Subjects** | **Risk of Bias**  **Design/ Quality** | | | **Consistency** | | **Directness** | **Precision** | | **Results** | | **Strength of Evidence** |
| **Other Adverse Events:**  **Oral DMARD vs. Oral DMARD**  1 RCT  N = 795  3 observational  N = 80,332  1 review  N = 366 | | Medium  RCT/1 good;  observational/ 3 fair;  review 1 fair | Unknown, single studies | | Indirect | | Imprecise | Oral DMARDs increase risk of septic arthritis; LEF + corticosteroids increase risk of wound healing complications; no association of oral DMARDs with sinus problems; no increased risk of renal damage with combination; insufficient information on fertility, pregnancy, and lactation | | Low | |

DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; RCT, randomized controlled trial; SSZ, sulfasalazine.

\* Eligible RCTs included double-blind, randomized, placebo- or MTX-controlled trials lasting at least 12 weeks to determine comparative tolerability, safety, or efficacy. To be included, trials must have reported on at least one of the following: overall withdrawals, withrawals because of lack of efficacy, or withdrawals because of adverse events.