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

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| --- | --- | --- | --- | --- | --- | --- |
| **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 = 18391 observational N = 40,594; 3 meta-analysis N = 7,245 | LowRCTs/3 fairRetrospective cohort/1 fairmeta-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 observationalN = 3492 meta-analysis N = 1,735 | LowRCTs/2 good, 4 faircohort/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 = 12021 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)

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| **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 | Mediumobservational/ 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 | Mediumobservational/ 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 | Mediumobservational/ 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 | Mediumobservational/ 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 | Mediumobservational/ 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 | Mediumobservational/ 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)

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| --- | --- | --- | --- | --- | --- | --- |
| **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 = 7953 observational N = 80,3321 review N = 366 | MediumRCT/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.