# Efficacy of methotrexate monotherapy and combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis

NEWS

Pain Management

Methotrexate is regarded as the most favorable disease-modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA), but the debate arises on the additional benefits and harms of combining methotrexate with other DMARDs. Hence, the network meta-analysis explained in this study with an aim to distinguish methotrexate and methotrexate-based DMARD combinations for RA in patients naïve to or with an inadequate response (IR) to methotrexate.

All randomised controlled trials with methotrexate monotherapy or in combination with any conventional synthetic DMARD, biologic DMARDs, or tofacitinib were efficiently recognized. The assessment of three major outcomes (ACR50 response, radiographic progression and withdrawals due to adverse events) and multiple minor outcomes was done. Consequences of the treatment were reviewed using Bayesian random-effects network meta-analyses, separately for methotrexate-naïve and methotrexate-IR trials. Heterogeneity was investigated through meta-regression and subgroup analyses. Risk of bias of each trial was analysed via the Cochrane risk of bias tool, and trials at high risk of bias were excluded from main analysis. The GRADE approach was used to evaluate the quality of evidence. Comparison between treatments was considered statistically important if its credible interval prohibited the null effect, indicating >97.5% probability that one treatment was superior.

As per main outcomes, 158 trials with over 37,000 patients were inculcated. Methotrexate-naïve: Several treatment combinations with methotrexate were statistically superior to oral methotrexate for ACR50 response: methotrexate + sulfasalazine + hydroxychloroquine ("triple therapy"), methotrexate + several biologics (abatacept, adalimumab, etanercept, infliximab, rituximab, tocilizumab), and tofacitinib. The estimated probability of ACR50 response was indistinguishable between these treatments (range 56-67%), compared with 41% for methotrexate. The approximate mean change over one year with all treatments was less than minimal clinically important difference of five units on the Sharp-van der Heijde scale although methotrexate plus adalimumab, etanercept, certolizumab, or infliximab was statistically superior to oral methotrexate for inhibiting radiographic progression. Methotrexate + azathioprine had statistically more abolitions due to adverse events than oral methotrexate, and triple therapy had statistically fewer abolitions due to adverse events than methotrexate + infliximab (rate ratio 0.26, 95% credible interval: 0.06 to 0.91). Methotrexate-inadequate response: In patients with an inadequate response to methotrexate, several treatments were statistically significantly superior to oral methotrexate for ACR50 response: triple therapy (moderate quality evidence), methotrexate + hydroxychloroquine (low quality evidence), methotrexate + leflunomide (moderate quality evidence), methotrexate + intramuscular gold (very low quality evidence), methotrexate + most biologics (moderate to high quality evidence), and methotrexate + tofacitinib (high quality evidence). There was 61% probability of an ACR50 response with triple therapy, contrast to a range of 27% to 64% for combinations of methotrexate + biologic DMARDs that were statistically significantly superior to oral methotrexate. For inhibiting radiographic progression, no treatment was statistically significantly superior to oral methotrexate. Methotrexate + cyclosporine and methotrexate + tocilizumab (8 mg/kg) had a statistically higher rate of withdrawals due to adverse events than oral methotrexate and methotrexate + abatacept had a statistically lower rate of withdrawals due to adverse events than various treatments.

A moderate to high quality evidence was obtained depicting that combination therapy with methotrexate + sulfasalazine+ hydroxychloroquine (triple therapy) or methotrexate + most biologic DMARDs or tofacitinib were similarly effective in curbing disease activity and generally well tolerated in methotrexate-

naïve patients or after an inappropriate response to methotrexate. Methotrexate + some biologic DMARDs were superior to methotrexate in averting joint damage in methotrexate-naïve patients, but the magnitude of these consequences was small over one year.

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