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Background: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease potentially leading to disability, impaired functioning, and premature death. Most treatment strategies include the early use of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) which is considered as an established 'anchor' therapy. Since it takes some weeks until MTX shows clinical efficacy, glucocorticoids (GC) are widely used for bridging.

Objectives: The aim of the study "Comparison of the efficacy and safety of two starting dosages of prednisolone in early active RA" (CORRA) is to compare the efficacy and safety of two standard GC bridging schedules vs. placebo in addition to MTX, following a treat-to-target regimen, in early RA.

Methods: CORRA is an investigator-initiated, randomised, multi-center, double-blind, placebo-controlled trial. Adult RA patients who were eligible for inclusion in the trial if they had a disease duration of less than 3 years and moderate or high disease activity were recruited in one hospital and 18 rheumatology practices in Germany. Patients were randomised (1:1:1) to receive 60mg or 10mg prednisolone (Pred) orally once daily (tapered down to 5mg Pred within 8 weeks) or placebo. The duration of the intervention was 12 weeks, followed by an open observational phase for another 40 weeks. All patients were also treated with MTX (usually starting with 15mg/week followed by a treat-to-target scheme). The primary efficacy endpoint was the progression of the radiographic joint damage after one year compared to baseline as determined by the van der Heijde modification of the Sharp score (SHS). Patients, physicians and readers of radiographs were unaware of the treatment assignments. For the comparison of the two GC groups, a non-inferiority margin of 1.3 points of the SHS was set. This trial was registered at ClinicalTrials.gov, number NCT02000336.

Results: Between February 2014 and February 2017, 395 patients were included in the trial, 381 of which had sufficient data also of follow-up visits. A total of 129 patients were assigned to the 60mg Pred group, 124 to 10mg Pred and 128 to the placebo group. At baseline, mean age was 58 years, 58% were female, 55% were rheumatoid factor and 52% ACPA positive. The mean number of swollen joints was 12.8 out of 28, mean ESR was 33.6mm/h, mean CRP 2.2mg/dL, mean DAS 28 6.0. Radiographic damage was 4.9 as measured by the SHS. In the 60mg, 10mg Pred group and in the placebo group, the DAS 28 was 2.6, 3.1, 4.5 at week 4 ($p<0.001$), 3.1, 2.8, 3.6 at week 12 ($p<0.001$), and 2.7, 2.6, 2.8 at week 52 ($p=0.411$), respectively. After 12 months the radiographic progression could be determined in 375 patients. In the 60mg, 10mg Pred group, and in the placebo group, the mean progression after 1 year was 1.0, 1.0, 1.1 for the total SHS and 0.5, 0.6, 0.7 for the erosion score of the SHS, respectively. Statistical analysis showed non-inferiority of the 10mg Pred and of the placebo group in comparison to the 60mg Pred group. Regarding safety issues, there were 10, 5, 6 serious adverse events and 31, 16, 20 adverse events in the MedDRA system organ class "infections and infestations" for the 60mg Pred, 10mg Pred, and the placebo group, respectively.

Conclusion: The bridging schedule starting with 60mg Pred reduced disease activity better than the 10mg schedule or placebo only for a short time. The primary outcome structural damage was non-inferior in the 10mg Pred and the placebo group in comparison to the 60mg Pred group. Initial advantages of the higher dose may have been compromised by the long follow-up with the possible escalation of therapy due to the treat-to-target regimen.

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SAT0136

RELATIVE EFFICACY AND SAFETY OF TOFACITINIB, BARICITINIB, UPADACITINIB, AND FILGOTINIB, IN COMPARISON WITH ADALIMUMAB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: A BAYESIAN NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Methotrexate (MTX), an effective disease-modifying antirheumatic drug (DMARD) [2], is the most widely used DMARD for the treatment of rheumatoid arthritis (RA). However, not all patients are responsive to the drug; 30% of the patients discontinue therapy within 1 year of commencing the treatment, usually because of the lack of efficacy or undesirable adverse effects. Small-molecule Janus kinase inhibitors are clinically developed for the treatment of RA.

Objectives: The aim of this study is to investigate the relative efficacy and safety of tofacitinib, baricitinib, upadacitinib, and filgotinib in comparison with adalimumab in patients with active RA and having inadequate responses to MTX.

Methods: We performed a Bayesian network meta-analysis to combine direct and indirect evidence from randomized controlled trials (RCTs) to examine the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib, and adalimumab in RA patients having inadequate responses to MTX.

Results: Four RCTs, comprising 5,451 patients, met the inclusion criteria. The baricitinib 4mg+MTX and upadacitinib 15mg+MTX group showed a significantly higher American College of Rheumatology 20% (ACR20) response rate than the adalimumab 40mg+MTX group. The ranking probability based on the surface under the cumulative ranking curve (SUCRA) indicated that baricitinib 4mg+MTX had the highest probability of being the best treatment for achieving the ACR20 response rate, followed by upadacitinib 15mg+MTX, tofacitinib 5mg+MTX, filgotinib 200mg+MTX, filgotinib 100mg+MTX, adalimumab 40mg+MTX, and placebo+MTX. The upadacitinib 15mg+MTX and baricitinib 4mg+MTX groups showed significantly higher ACR50 and ACR70 response rates than adalimumab 40mg+MTX. In terms of Herpes zoster infection, the ranking probability based on the SUCRA indicated that placebo+MTX were likely to be the safest treatments, followed by filgotinib 200mg+MTX, filgotinib 100mg+MTX, adalimumab 40mg+MTX, tofacitinib 5mg+MTX, upadacitinib 15mg+MTX, and baricitinib 4mg+MTX. Regarding safety analysis, no statistically significant differences were found between the respective intervention groups.

Conclusion: In RA patients with an inadequate response to MTX, baricitinib 4mg+MTX and upadacitinib 15mg+MTX showed the highest ACR response rates, suggesting a difference in efficacy among the different JAK inhibitors.

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METHOTREXATE ASSOCIATED ADVERSE EVENTS AND THEIR PREDICTORS IN METHOTREXATE-NAÏVE PATIENTS WITH RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

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Background: The adverse events (AEs) associated with methotrexate (MTX) treatment for rheumatoid arthritis (RA) have been studied extensively, but precise estimates of the incidence and prevalence of AEs are lacking. There is also limited published data on the predictors of AEs.

Objectives: To summarise and pool incidence and prevalence rates of AEs in patients treated with MTX for RA, and to identify treatment, clinical and disease related predictors of AEs.

Methods: A systematic literature search was carried out using Embase, Medline, and CENTRAL databases to identify relevant studies published between 1/1/2005 and 12/2/2019. The eligibility criteria included RCTs, non-randomized trials, and observational studies of first-time users of MTX in adults (≥ 18 years old) with RA and reported incidence, prevalence or predictors of the most common MTX related AEs, including: any AE, serious AEs, discontinuation due to AEs, elevated liver enzymes, gastrointestinal (GI), mucocutaneous (MC), central nervous system (CNS), and pulmonary AEs. Pooled proportions of GI AEs and elevated liver enzymes of patients treated with MTX monotherapy were estimated using random effects meta-analysis.

Results: Of 3142 records screened, we included 46 articles (35 clinical trials and 11 cohort studies) with a total of 9646 patients, and a mean follow-up duration of 70 $\pm$ 35 weeks (range: 13 - 104 weeks for RCTs, 40 - 156 weeks for observational cohorts). Six studies reported incidence rate (IR) of any AE (range: 196 - 595 per 100 person-years), and eight studies reported IR of serious AEs (range: 3.7 - 15.9 per 100 person-years). The percentage of patients with any AE, reported in 32 studies, varied between 37% and 100% in RCTs, and between 13% and 34% in observational studies. Discontinuation of MTX due to AEs ranged between 1% and 29% in RCTs, and between 8% and 38% in observational studies. The reported prevalence of MC events (4% - 54%), CNS events (12% - 59%) and pulmonary events (10% - 67%) varied between studies.

The estimated pooled prevalence from studies with a MTX monotherapy arm was 14% (95% CI: 9%, 19%; N=7 studies) for liver enzymes elevation (Figure 1), and 29% (95% CI: 13%, 44%; N=7 studies) for GI AEs (Figure 2).

Figure 1. Forest plot of pooled prevalence of elevated liver enzymes

Figure 2. Forest plot of pooled prevalence of gastrointestinal adverse events

No statistically significant predictors of "any AE" were identified. For discontinuation of MTX due to AEs, RF positivity was associated with lower risk of MTX discontinuation due to MTX (HR 0.37, 95%CI: 0.21, 0.64), while other studies found that baseline HAQ score (OR 1.87, 95%CI: 1.11, 3.15) and BMI (OR 1.21, 95%CI: 1.02, 1.44) were associated with increased risk of MTX discontinuation due to AEs.

ACPA positivity (OR 1.8, 95%CI: 1.1, 3.1), and high baseline alanine aminotransferase (ALT) (OR 3.1, 95%CI: 1.6, 6.2) were both independent predictors of two-fold elevation of ALT in one paper, and baseline creatinine (OR 1.03, 95%CI: 1.00, 1.07) and high baseline ALT (OR 1.03, 95%CI: 1.00, 1.06) were associated with increased risk of elevated ALT above the upper limit of normal in a different study.

Conclusion: These findings affirm the high prevalence of GI AEs and elevated liver enzymes among patients treated with MTX for RA. The identified predictors of MTX withdrawal and elevated ALTs may be useful for identifying future patients likely to experience these AEs early in the course of treatment. However, the results of the predictors should be interpreted with caution, and further work is needed to replicate the results in studies with larger sample sizes and to assess the prognostic value of established predictors.

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SAT0138 DRUG-RELATED PANCYTOPENIA AND LEUKOPENIA IN RHEUMATOID ARTHRITIS: ARE ALL CSDMARDS EQUAL?

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Background: Cytopenia is a known side-effect of conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) in rheumatoid arthritis (RA). There is a lack of data on the comparative risk of cytopenia with different csDMARDs.

Objectives: To assess the comparative risk of leukopenia and pancytopenia for the most frequently used first-line csDMARDs: methotrexate (MTX), hydroxychloroquine (HCQ), sulphasalazine (SSZ), and leflunomide (LEF).

Methods: The study used data from 7 databases from 4 countries: CCAE, MDCR, Optum, IQVIA Ambulatory EMR (US); IQVIA THIN IMRD EMR (UK); IQVIA Disease Analyzer EMR (Germany); and SIDIAP (Spain). Cohorts included adult patients with a diagnosis of RA from 2005 to 2019 with at least one-year prior follow-up, no prior inflammatory arthritis, initiation of first-line csDMARD, and no cytopenia in the preceding 30 days. Participants were followed from one day after treatment initiation to the earliest of event occurrence, treatment discontinuation/switching plus 14 days in the on-treatment analysis, five years in the intent-to-treat (ITT) analysis, or loss to follow-up. MTX was used as reference group. Cox models were fitted with propensity score stratification for observed confounding and negative control outcomes calibration for residual error. Estimates across database were pooled where $I^2 < 40\%$ was seen.

Results: Overall 166,347 patients were included. Pooled rates of leukopenia and pancytopenia for MTX were 10.9 and 3.2 per 1,000 person years, respectively. Figure 1 and 2 show the results for the different databases and pooled estimates where applicable. Database estimates are not reported where adequate covariate balance not attained, and meta-analysis not shown where $I^2 > 0.4$. MTX showed slightly higher hazards of leukopenia and of pancytopenia compared to LEF but no consistently differential risks compared to HCQ or SSZ.

Figure 1. Calibrated hazard ratios (95% CI) vs MTX, on-treatment analysis

Conclusion: Cytopenia is rare, and apparently more frequent with MTX and less with LEF. Since prior full blood counts were inconsistently obtained in fewer than