(KO) mice were bred to generate homozygous KOs and mouse articular cartilage was isolated to culture chondrocytes.
Results: miR-34a expression was significantly elevated in the plasma as well as cartilage and synovium of TKR patients (KL IV) compared to healthy controls and early OA patients (KL-I), respectively. Similarly, miR-34a was significantly overexpressed in mouse knee joints (cartilage and synovium) at 10 weeks post OA surgery compared to sham. To identify the biological effects of miR-34a on chondrocyte and synovial fibroblast (SF), functional studies were conducted *in-vitro*. Chondrocytes treated with miR-34a mimic had a significant reduction of SIRT1 (a direct target of miR-34a), anabolic (type II collagen and aggrecan) and autophagy markers, as well as, elevated catabolic markers (MMP13), suggesting that miR-34a contributes to cartilage degeneration. Chondrocytes treated with mir-34a inhibitor reversed these destructive effects. SFs treated with miR-34a mimic expressed elevated inflammatory (TNF-α, IL-6), fibrotic (TGF-β, Type 1 Collagen), and autophagy markers, suggesting that miR-34a is involved in mediating synovial inflammation and fibrosis. SFs treated with miR-34a inhibitor reversed these effects.
In vivo, intra-articular injection of miR-34a mimic induced cartilage damage, loss of proteoglycan content, and elevated cell death markers (PARP p85 and Caspase 3) in the articular cartilage. To confirm the destructive effects of miR-34a in the articular cartilage, we used miR-34a KO mice. MiR-34a KO mice further confirmed that genetic ablation of miR-34a resulted in marked elevation in the expression of anabolic markers (type II collagen and aggrecan) and decreased expression of catabolic ADAMTS-5 in the articular cartilage.
To test the therapeutic potential of blocking miR-34a, we intra-articularly injected mir-34a inhibitor in mice subjected to OA surgery. Results showed marked reduction in the severity of cartilage degeneration in mice treated with miR-34a inhibitor.
Conclusion: This study, for the first time, demonstrates miR-34a as a crucial mediator involved in OA pathogenesis and as a potential therapeutic target for limiting cartilage destruction during OA.
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OP0019-HPR A SYSTEMATIC REVIEW AND META-ANALYSIS ASSESSING GASTROINTESTINAL, LIVER, RENAL AND CARDIOVASCULAR ADVERSE EVENTS OF PARACETAMOL

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Background: Despite its modest efficacy, guidelines consistently recommend paracetamol as a first-line analgesic for osteoarthritis (OA) based on its perceived safety. However, there is growing controversy, highlighted in the National Institute for Health and Care Excellence OA (NICE) 2014 guidance on OA, that paracetamol is not as safe as previously thought, especially at the highest therapeutic dose of 4gm/day.
Objectives: To investigate the association between paracetamol and gastrointestinal, liver, renal and cardiovascular adverse events both in randomised controlled trials (RCTs) and observational studies.
Methods: We systematically searched MEDLINE, EMBASE, PUBMED, AHMED, CINAHL, Web of Science, and Google Scholar for published literature in any language to the end of November 2018 for (1) RCTs of paracetamol in symptomatic OA, and (2) observational studies irrespective of any underlying condition, to determine the risk of gastrointestinal, liver, renal and cardiovascular adverse events. We included studies assessing oral paracetamol in people aged ≥18 years and reporting on clinically relevant adverse effects. Risk ratio (RR) and 95% confidence interval (CI) were estimated for RCT and cohort studies, whereas odds ratio (OR) and 95% CI were used for case-control studies. Results were pooled as appropriate using random effects model. The risk of bias was assessed using modified Cochrane tool for RCTS and Newcastle Ottawa scale for observational studies.
Results: We reviewed titles and abstracts of 3,622 records in the systematic search (1,997 RCTs and 1,635 observational studies). After examining full papers 23 RCTs (7,863 participants), 15 cohort studies (2,262,517 participants) and 34 case-control studies (441,638 participants) met inclusion criteria.
Compared to placebo, paracetamol was associated with increased incidence of treatment-related adverse events (RR 1.35, 95% CI 1.04 to 1.75), especially diarrhoea (RR 2.14, 95% CI 1.35 to 3.37) and abnormal liver function (RR 3.99, 95% CI 2.05 to 7.77). The pooled OR from twelve age and gender matched case-control studies (7894 participants) was 1.36 (95% CI 1.13 to 1.64) for upper gastrointestinal bleeding. In addition, a dose response relationship was observed in a cohort study (382,404 participants) for this outcome. The RR was 1.11 (95% CI 1.04 to 1.21) with low dose paracetamol (measured as medication possession rate) and 1.49 (95% CI 1.29 to 1.71) with high dose paracetamol. Paracetamol was not associated with cardiovascular events in two RCTs (775 participants) (RR 1.27, 95% CI 0.06 to 27.77) and three case-control studies (42,180 participants) (OR 0.97, 95% CI 0.77 to 1.21), but in three cohort studies (208,926 participants) (RR 1.35, 95% CI 1.14 to 1.59). There were insufficient data in RCTs and case-control studies for renal adverse events. However, three cohort studies (7,360 participants) demonstrated a dose response relationship between paracetamol and renal function impairment (defined as ≥30 percentage decrease in estimated glomerular filtration rate). The data of these three cohort studies could not be pooled due to different doses of paracetamol. One cohort study (1697 participants) reported RR of 1.40 (95% CI 0.79 to 2.48) for renal impairment for paracetamol 100-499g, and 2.19 (95% CI 1.4 to 3.43) for paracetamol >3000g.
Conclusion: Paracetamol is associated with diarrhoea and abnormal liver function in short-term trial data, and with upper GI bleeding and renal impairment in long-term observational data. Methodological limitations of observational data, such as channelling bias, may confound the results. Large-scale well-designed prospective studies are needed to ascertain the long-term safety of paracetamol.
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OP0020 LESS IS MORE: ANA-LYSING THE IMPACT OF REPEATED ANTINUCLEAR ANTIBODY TESTING

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Background: Minimising unnecessary tests is a global health economic priority with multiple initiatives in place to avoid inappropriate healthcare utilisation(1) and harm. Anti-nuclear antibody (ANA) testing is frequently performed as a diagnostic test for autoimmune conditions, such as systemic lupus erythematosus (SLE) or as a screening test in patients with inflammatory or musculoskeletal symptoms. The value of serial testing in the monitoring of such conditions is unclear and false positive tests can lead to unnecessary further investigation and increased patient anxiety(2)
Objectives: To evaluate the frequency of repeated ANA testing as a prelude to Electronic Medical Record (EMR) test alert design in an Australian healthcare network. The primary endpoint was calculation of the total cost associated with repeated testing and whether a longitudinal change in ANA resulted in any new ANA associated rheumatological diagnoses. Our secondary endpoint was the examination of baseline ANA testing behaviours.
Methods: We retrospectively analysed data from a multi-centre tertiary health network in Melbourne, Australia across a 7-year period (19 March 2011 to 23 July 2018). ANA and other autoimmune test results were obtained from the hospital pathology system with a positive ANA cut off set at 1:160. Clinical information was sourced from clinical information systems on patients who had a change in ANA result from negative to positive on repeat testing. The associated cost of repeated ANA testing was calculated based on the baseline cost to the public system.
Results: A total of 36,715 ANA tests (excluding 980 cancelled same-day requests) were performed in 28,840 patients. Of these, 14,058 (38.3%) were positive with females accounting for 9,265 (65.9%, p<0.001). The most frequent ANA patterns were homogenous (47.4%) and nucleolar (23.3%). ANA titres were as follows; 1:160 (41.4%), 1:320 (15.3%), 1:640 (13.1%) and 1:1280 (29.2%). 7,875 (21.4%) of tests were repeat tests. Of these 511 (6.5%) results changed from negative to positive. The median time between a negative ANA result to the first positive result was 1.71 years (IQR 0.50-3.55). Clinical information was captured for a median duration of 1.24 years (IQR 0.50-2.07) following a positive ANA result. A change to positive ANA was associated with a new ANA-associated rheumatological diagnosis in only 5 cases (2 SLE, 1 scleroderma and 2 undifferentiated connective tissue disease) with a positive predictive value calculated at 0.01. When comparing patients who with a new diagnosis to those with no new diagnosis, there was no difference between ANA titre, pattern, duration to first positive ANA, ordering location or clinician, or age of first positive ANA test. The direct total cost for the government of all ANA testing was AUD$903,189, of which repeat testing contributed AUD$193,725.
Conclusion: Repeat ANA testing after a negative result had limited utility in the diagnosis of ANA associated rheumatological conditions with a positive predictive value of only 0.01, and resulted in high cost. New technology and clinical alert systems may help reduce unnecessary testing with potential significant direct cost savings when extrapolated across the Australian healthcare system.

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OP0021 PREDICTING SEVERE INFECTION IN REPEAT CYCLES OF RITUXIMAB AND EFFECTS OF HYPOGAMMAGLOBULINAEMIA FOR THE TREATMENT OF RHEUMATIC AND MUSCULOSKELETAL DISEASES

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Background: Rituximab (RTX) is effective in treating various rheumatic and musculoskeletal diseases (RMDs). Repeat cycles are often required for disease control but may lead to hypogammaglobulinaemia. Low IgG at baseline has been associated with increased risk of severe infection event (SIE) post-RTX. However, there are limited data on predictors of SIEs in repeat cycles including immunoglobulin levels and B-cell numbers as well as outcomes of hypogammaglobulinaemia.
Objectives: To assess predictors of SIEs in repeat RTX cycles and effects of hypogammaglobulinaemia in terms of SIEs rates, humoral response and its persistence post-cessation of RTX.
Methods: A retrospective study was conducted in the first 700 consecutive ARD patients treated with at least a cycle of RTX in Leeds. IgM, IgA and IgG levels were measured at baseline and 4-6 months after each cycle. For cycles 2-4 (C2-4), predictors for SIEs were analysed using mixed-effects logistic regression analysis.
Results: 550 patients were female, mean(SD) age 56(16) years and median (IQR) disease duration 7.9(3.4-15.0) years. 507(72%) had RA, 94(13%) SLE, 49 (7%) AAV, 14(2%) inflammatory myopathies, 9(1%) pSS, 5(1%) APS, 6(1%) SSc and 16(3%) other CTDs. 364(52%) were biologic-naïve and 514(73%) were on concomitant DMARDs. Total follow-up: 2880 patient-years (PY). 281 SIEs were recorded in 176 patients (9.8/100 PY). In C1, we had validated that low IgG was predictive of SIE within 12 months of C1. For cycles 2-4, in multivariable analysis, non-RTX-specific comorbidities [chronic lung OR (95% CI) 2.4 (1.3-4.4), diabetes 2.9 (1.2-6.9), heart failure 6.3 (1.4-28.1), previous cancer 3.0 (1.3-6.7) and severe infection 6.3 (3.0-13.4)] and RTX-specific variables [higher corticosteroid dose 1.08 (1.02-1.14), higher IgM 1.3 (1-1.7) and longer retreatment time 1.01 (1-1.02)] were associated with increased odds of SIEs, but not B-cell numbers or depletion status. Higher IgG reduced the risk 0.88 (0.8-0.96). Of 103 patients with low IgG for at least 4 months duration, SIEs rates were higher in those with low baseline IgG (16.4 PY) or acquired it during/post-RTX (21.3 PY) versus those with normal IgG (9.7 PY), 5/8(64%) had impaired humoral response to pneumococcal and haemophilus following vaccination challenge and only 4/11(36%) had IgG normalised after switching therapies. Overall, 7(1%) of the patients required Ig replacement based on recurrent sino-pulmonary SIEs and/or low IgG.
Conclusion: Immunoglobulin should be monitored at baseline and before each RTX cycle to identify patients at risk of SIEs. Vigilance is needed for those with lower IgG as this is a consistent predictor of SIE and may affect infection outcomes when patients are switched to a different bDMARD. For those at risk of SIEs, reduction of corticosteroid dose could reduce risk. Low B-cell numbers were not predictive of SIEs.
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OP0022 DO MRI-DETECTED EROSIONS IN PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA PREDICT PROGRESSION TO RHEUMATOID ARTHRITIS? A LONGITUDINAL STUDY

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Background: Radiographic joint erosions are a hallmark of Rheumatoid Arthritis (RA). MRI is more sensitive than radiographs in detecting erosions. It is unknown if MRI-detected erosions are predictive for RA-development in patients with Clinically Suspect Arthralgia (CSA).
Objectives: We investigated the prognostic value of MRI-detected erosions (any MRI-erosion, or MRI-erosion characteristics that were recently identified as specific for RA) in CSA.
Methods: Patients presenting with CSA (n=491) underwent contrast-enhanced 1.5T MRI of the wrist, metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints at baseline. MRIs were scored according to RAMRIS. Presence of any MRI-erosion (erosion score $\geq$1) and RA-specific erosion characteristics as identified previously (grade $\geq$2 erosions, erosions in MTP5, erosions in MTP1 if aged <40) were studied with clinically apparent inflammatory arthritis development as outcome (median follow-up 17 months). Analyses were corrected for age, CRP, ACPA and MRI-detected inflammation.
Results: Erosions were present in 20.6% of patients. Presence of erosions was not associated with arthritis development (HR multivariable analysis 0.85 (95% CI 0.52-1.40)). Also the different erosion characteristics were not predictive in CSA-patients (grade $\geq$2 HR 1.29 (95% CI 0.40-4.14), erosions in MTP5 HR 0.89 (95% CI 0.38-2.09) and MTP1 if aged <40 HR 0.98 (95% CI 0.23-4.21)). MRI-erosions were more prevalent in ACPA-positive than in ACPA-negative patients (32.3% versus 18.8%, p=0.02). However, no association with arthritis development was observed in both subgroups.
Conclusion: MRI-detected erosions in hands and feet of patients with CSA were not predictive for arthritis development. These data warn against overinterpretation of MRI-detected erosions in CSA.
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LB0001 EFFICACY AND SAFETY OF FILGOTINIB FOR PATIENTS WITH RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO METHOTREXATE: FINCH1 PRIMARY OUTCOME RESULTS

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Background: Filgotinib (FIL) is an orally administered, potent and selective inhibitor of Janus kinase 1 (JAK1) that has shown good efficacy and was well tolerated for treatment of rheumatoid arthritis (RA).
Objectives: To evaluate efficacy and safety of FIL treatment in patients with RA who have had an inadequate response to methotrexate (MTX).