OP0019-HPR

A SYSTEMATIC REVIEW AND META-ANALYSIS ASSESSING GASTROINTESTINAL, LIVER, RENAL AND CARDIOVASCULAR ADVERSE EVENTS OF PARACETAMOL

Jaspreet Kaur, Burak Kundaki, Georgina Nakafero, Abhishek Abhishek, Michael Doherty, Weiya Zhang. University of Nottingham, Academic Rheumatology, Nottingham, United Kingdom

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.

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 events. 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 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 (208,928 participants) (RR 1.35, 95% CI 1.14 to 1.59).

Conclusion: This is the first time, demonstrates paracetamol as a crucial mediator involved in OA pathogenesis and as a potential therapeutic target for limiting cartilage destruction during OA.

Disclosure of Interests: None declared

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Disclosure of Interests: Al Li Yeo: None declared, Jason Ong: None declared, Kathryn Connelly: None declared, Suong Le: None declared, Ronnie Ptasznik: None declared, Jane Ross: None declared, Eric F. Morand Grant/research support from: Roche, Pfizer Ltd, UCB, Consultant for: AbbVie; Eli Lilly, EMD Serono, Pfizer Ltd. Sanofi, Paul Emery Grant/research support from: Pfizer, MSD, AbbVie, Bristol-Myers Squibb, Roche, Consultant for: Pfizer, MSD, AbbVie, Bristol-Myers Squibb, UCB, Roche, Novartis, Gilead, Samsung, Sandoz and Lilly.

Sivac Grant/research support from: Novartis and Sobi

OP0021
PREDICTING SEVERE INFECTION IN REPEAT CYCLES OF RITUXIMAB AND EFFECTS OF HYPOGAMMAGLOBULINAEMIA FOR THE TREATMENT OF RHEUMATIC AND MUSCULOSKELETAL DISEASES
Md Yuzafalid Md Yusof1,2, Edward Vital1,2, Damien M McElvenny3, Elizabeth Henson1,2, Sudipto Das1,2, Shouvik Dass1, Andy C. Rawstron1, 4, Maya Buc1,2, Paul Emery1,2, Sinisa Savic1,2, 1University of Leeds, Leeds Institute of Rheumatology and Musculoskeletal Medicine, Leeds, United Kingdom; 2Leeds Teaching Hospitals NHS Trust, NIHR Leeds Biomedical Research Centre, Leeds, United Kingdom; 3Leeds Institute of Health Care Sciences, University of Leeds, Leeds, United Kingdom; 4Department of Medicine, Leeds Teaching Hospitals NHS Trust, University Health Networks, Leeds, United Kingdom

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 (4.3-14.5) years. 502 (72%) had RA, 94 (13%) SLE, 49 (7%) AAV, 14 (2%) inflammatory myopathies, 9 (1%) pSLE, 5 (1%) APS, 6 (1%) SSC and 47 (7%) other connective tissue diseases. 56 (65%) were biologic-naive and 51 (73%) were on biocompatible-manufactured MTX at baseline. 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 (1.1-1.7) and longer retardment time 1.01 (1.01-2) 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), 5.9 (96%) had impaired humoral response to pneumococcal and haemophilus following vaccination challenge and only 4/11 (36%) had IgG normalised after switching therapies. Overall, 71% 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.

Acknowledgement: This research was supported by Octapharma and NIHR (DRF-2014-07-15). The views expressed are those of the authors (s) & not necessarily the NHS, NIHR or DOH.

Disclosure of Interests: Md Yuzafalid Md Yusof: None declared, Edward Vital Grant/research support from: He has received honoraria and research grant support from Roche, GSK and AstraZeneca., Damien M McElvenny: None declared, Elizabeth Henson: None declared, Sudipto Das: None declared, Shouvik Dass Grant/research support from: Roche and GSK, Andy C. Rawstron: None declared, Maya Buc: None declared, Elizabeth Henson: None declared, Sudipto Das: None declared, Damien M McElvenny: None declared, Md Yuzaiful Md Yusof: None declared, Edward Vital: None declared, Paul Emery: None declared, Sinisa Savic: None declared, Damien M McElvenny: None declared, Sudipto Das: None declared, Shouvik Dass: None declared.