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POS0661

RAPID RESPONSE TO BARICITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO METHOTREXATE AND AT LEAST ONE BIOLOGIC DMARD: A CLINICAL AND POWER DOPPLER ULTRASOUND STUDY

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Background: Baricitinib, an oral Janus kinase (JAK) 1-2 inhibitor, is currently used among biologic DMARDs (bDMARDs) after the failure of methotrexate (MTX) in rheumatoid arthritis (RA). Power Doppler ultrasound (PDUS) is a promising, non-invasive imaging method to assess synovitis in RA: results from numerous studies suggest that it provides additional information to clinical and conventional radiographic examinations.

Objectives: The main objective of our study was to evaluate short-term efficacy of Baricitinib in reducing synovitis, using the composite semi quantitative scale (0-3 grades) PDUS synovitis score, developed by the Outcome Measures in Rheumatology- European League Against Rheumatism (OMERACT-EULAR)-Ultrasound Task Force. Moreover both synovial hyperplasia and intrasynovial power Doppler (PD) signal were also scored as single components/parameters on 0-3 scales. Secondary objective was to assess the concordance between patient reported outcomes (PROs), markers of inflammation, physical examination and US.

Methods: We enrolled 30 patients fulfilling 2010 ACR and EULAR criteria for RA. All patients had failed at least one anti-TNF. Each patient was prescribed Baricitinib 4mg/daily at T0, in addition to MTX and/or oral steroids at a dosage ≤ 7.5 mg/day of Prednisone or equivalent, at T: All patients were evaluated at baseline (T0) and then after one month (T1), 3 months (T2) and 6 months (T3) of treatment. Swollen and tender joints (out of 28) were evaluated and recorded, as well as patient (PGA) and physician global assessment (PhGA) and pain, expressed in a visual analog scale (VAS). Disease activity was evaluated at each visit using DAS28 (Disease activity score 28), CDAI (Clinical disease activity index) and SDAI (Simplified disease activity index), accompanied by a complete blood count, Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) collection. Statistical analysis was performed using GraphPad version 9.0.0. PDUS examination, was carried out by two rheumatologists (PF and CB) blinded to clinical conditions of the patients, using an Esaote Mylab Twice (Genoa, Italy), equipped with a high-frequency (6-18 MHz) linear probe. With standardised Doppler parameters (pulse repetition frequency between 500-750 Hz; Doppler frequency between 7-11.1 MHz). PDUS was performed at each visit bilaterally for 22 joint sites [MCPs 1-5, proximal interphalangeal joints (PIPs) 1-5, wrist, elbow, glenohumeral, knee, tibiotaral, talonavicular and calcaneocuboidal and metatarsophalangeal joints (MTPs) 1-5] for a total of 44 joints for each patient.

Results: We observed a reduction of VAS pain (T0 vs. T6 $p < 0.0001$) PDUS composite score (T0 vs. T6 $p < 0.0001$), Power Doppler (T0 vs. T6 $p < 0.0001$) synovial hyperplasia (T0 vs. T6 $p = 0.0002$), CRP (T0 vs. T6 $p < 0.0001$) and ESR (T0 vs. T6 $p < 0.0001$) was observed in our patients. Accordingly, DAS-28, CDAI and SDAI displayed a significant reduction too (DAS-28: T0 vs. T6 $p < 0.0001$; CDAI: T0 vs. T6 $p < 0.0001$; SDAI: T0 vs. T6 $p = 0.0003$).

Conclusion: We investigated the efficacy of Baricitinib in real life, evaluating both from a clinimetric and ultrasound point of view. Baricitinib demonstrated a significant parallel and fast improvement in VAS, PDUS and CRP was found at follow up assessment as early as one month of therapy. In conclusion, these results demonstrated the short term efficacy of Baricitinib 4mg for up to 6 months and providing a prompt improvement of PROs within the first weeks of treatment.

Figure 1. The difference between the means of PD and of the VAS pain over time (T0, T1, T3 and T6). Power Doppler (T0 vs. T6** $p < 0.0001$), VAS: (T0 vs. T1 * $p < 0.0098$; T0 vs. T3 **** $p < 0.0001$; T0 vs. T6 **** $p < 0.0001$)

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POS0662

PREDICTORS OF TOXICITY WITH HYDROXYCHLOROQUINE AND CHLOROQUINE USE: A SYSTEMATIC REVIEW

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Background: Hydroxychloroquine (HCQ) has attracted much attention especially during the COVID-19 pandemic. HCQ and closely related chloroquine (CQ) have known ocular and cardiac toxicity. However, although screening guidance now exists from the Royal College of Ophthalmologists for the former (RCOphth)¹, little is known regarding predictors of both forms of toxicity.

Objectives: To systematically explore the literature on predictors of toxicity limited to cardiac and ocular toxicity.

Methods: A detailed search of the following databases was conducted: PubMed, Medline, Embase, Web of Science, The Cochrane library, EMCare and Academic Search Premier. Studies addressing predictors of HCQ toxicity with relevant search terms used were included. Exclusion criteria were: non-English articles, pre-clinical and paediatric studies. Three authors (SR, NC, PK) independently screened titles and abstracts for inclusion, ensuring each article was screened twice. Disagreement over inclusion was adjudicated by senior reviewers (EN, JG). Data extraction (SR, NC, PK) focused on predictors of toxicity.

Results: The search strategy retrieved 3103 studies. 147 studies were included for data extraction, of which 92 were eventually excluded due to: not identifying predictors (n=17), reviews (n=19), not ocular or cardiovascular toxicity (n=18), case reports (n=3), paediatrics (n=1), screening articles that focused on detecting retinopathy (n=30), article unobtainable at time of abstract submission (n=4), leaving 55 studies for full review.

Studies addressing cardiac toxicity (n=16) included: cohort, retrospective observational, a comparative pharmacovigilance, systematic monitoring protocol and a randomised control trial (RCT). The majority of these involved high-dose (>5mg/kg/day) use for acute COVID-19 infection. The main significant predictors identified were: Hydroxychloroquine (HCQ) use in combination with azithromycin (6/7 studies), cumulative dose (2 studies), pre-existing cardiovascular morbidity (2/3 studies) and prolonged baseline QTc (2 studies). Individual associations were also identified in the following: longer treatment duration, daily dosage, increased age, male gender, severe COVID-19 infection, abnormal liver function tests (LFTs) and concurrent use of loop-diuretics.

Regarding predictors of ocular toxicity (n=39), only one study was a RCT. The remainder were observational studies: case-control, cohort, retrospective chart reviews and letters to the editor which included original patient data.

Several predictors of retinopathy and maculopathy were examined in two or more studies and included: duration of use (16/18 studies), daily dosage (7/13 studies), cumulative dose (11/14 studies), increased age (10/11 studies), body weight or BMI (3/5 studies), renal impairment (5 studies), HCQ blood levels (2 studies),

keratopathy (2 studies) and tamoxifen use (2 studies). Sex (2 studies) and history of cataract surgery (2 studies) were not found to be predictors of toxicity. Only few studies performed regression analysis presenting odds and/or hazard ratios with confidence intervals.

Conclusion: The most recognised predictor of cardiac toxicity was co-administration with azithromycin. In ocular toxicity, commonly cited predictors included those already recognised by the RCOPhth¹, as well as cumulative dose, increased age, weight considerations, HCQ blood levels and keratopathy. Further research is warranted on better characterising predictors of cardiac and ocular toxicity in patients on HCQ and CQ therapy.

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SAFETY AND EFFICACY OF COMBINING METHOTREXATE AND LEFLUNOMIDE AMONG PATIENTS WITH INFLAMMATORY ARTHROPATHIES: FINDINGS FROM THE PRIME REGISTRY

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Background: Currently, conventional synthetic DMARDs (csDMARDs) are the most commonly prescribed drugs as first-line treatment for peripheral arthritis. In resource-constrained settings where biologic agents are not widely available, there are limited therapeutic options for patients with rheumatoid arthritis (RA) and seronegative inflammatory arthropathies refractory to other csDMARD therapies. Hence, in our practice, we are inclined to use combination of potent DMARDs after MTX failure, prior to considering biologic therapies. We believe that combination of DMARDs, especially combining MTX and Leflunomide (LEF) provides a potent and valuable low-cost treatment option. Efficacy of MTX and LEF is very well established, but there have been lot of concern as regards their combination use due to potential risk of hepatotoxicity.

Objectives: We aimed to review our inflammatory arthropathies cohort data especially examining the safety, efficacy and drug retention of the combination usage of MTX and Leflunomide. We addressed this question using real-world data from the PRIME registry.

Methods: This was a cross-sectional study conducted using data collected at the time of patient enrolment in the PRIME registry. The PRIME Registry is a large, independent, prospective, observational cohort initiated in October 2019 that comprises patients diagnosed with RA, SLE, PsA or AS by a rheumatologist, and is being actively followed up. IRB approval and informed consent was obtained. A number of clinical variables were recorded. Detailed history was gathered from every patient regarding their present and past medications usage. Questions were asked directly about the usage or otherwise of all available DMARDs and biologics. The duration of usage, any adverse events, and the reasons for discontinuation were recorded. Evaluation of disease activity and severity was made as per internationally agreed definitions.

Results: The data of 766 inflammatory arthritis patients (RA=663, PsA=103) was reviewed. Among them, 241 patients (RA=196, PsA=45) were using combination therapy of MTX and LEF (combo MTX+LEF) with mean age 42.3±6 years; 42% male]. These patients had failed MTX or LEF monotherapy. Among these 241 patients, 49 patients were also on concomitant hydroxychloroquine therapy. It was noted that median drug retention of combo MTX+LEF therapy has been 9.5 months (IQR 6-16). Regarding any adverse events of combo MTX+LEF therapy, hepatotoxicity (ALT ≤3 times the upper limit of normal) was noted among 15 (6.2%) patients, hepatotoxicity (ALT ≥3 times the upper limit of normal) was noted among 8 (3.3%) patients, and troublesome gastrointestinal upset (nausea, or vomiting, or diarrhoea) in 3 (1.2%). Overall, only 13 (5.4%) patients had to discontinue this combo MTX+LEF therapy due to adverse events. Disease activity among combo MTX+LEF users was as follows: 64% (n=29) of PsA patients had achieved MDA; 42% (n=83) of RA cohort were in DAS28 remission, 46% (n=91) of RA patients were having DAS low disease activity.

Conclusion: Combination of MTX and LEF was well tolerated and had good drug retention time, with 94.6% of patients having ongoing treatment to date. In low-income countries, where bDMARD availability is limited, financial arguments significantly influence decision making process, and our data provides initial evidence that MTX and LEF combination therapy could be an effective treatment option.

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POS0664

A MULTICENTER RANDOMIZED STUDY IN RHEUMATOID ARTHRITIS TO COMPARE IGURATIMOD, METHOTREXATE, OR COMBINATION: 52 WEEK EFFICACY AND SAFETY RESULTS OF THE SMILE TRIAL

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Background: Igaratimod (IGU) has demonstrated efficacy and safety for active rheumatoid arthritis (RA) patients in double-blind clinical trials in China and Japan as a new disease-modifying anti-rheumatic drug (DMARD). There are no studies evaluating the radiographic progression of structural joint damage of IGU for the treatment of RA using the mTSS as the primary endpoint.

Objectives: Our study was to evaluate the efficacy and safety of IGU monotherapy and IGU combined methotrexate (MTX) compared with MTX monotherapy, including the inhibitory effects of joint destruction.

Methods: This randomized, double-blind, parallel-controlled, multicenter study in patients with active RA who have not previously used MTX and biological DMARDs (bDMARDs) (ClinicalTrials.gov Identifier NCT01548001) was carried out in China. Patients were randomized 1:1:1 to receive IGU 25mg twice a day (bid), MTX 10mg once a week(qw) for the first 4 weeks and 15mg once a week(qw) for week 5 to 52, or IGU combined MTX (IGU+MTX) for 52 weeks. The primary endpoints were to assess and compare American College of Rheumatology 20% (ACR20) response and the change of modified total Sharp scoring (mTSS) score over 52 weeks (Intention-to-treat, ITT analysis). The non-inferiority test was used to analyze the difference of ACR20 response at 52 weeks between the IGU monotherapy and the MTX monotherapy arms, and the non-inferiority