OP0016 INCREASED FREQUENCY OF ANTI-DRUG ANTIBODIES IN PATIENTS CARRYING COMPATIBLE IGG1 ALLOTYPES AND TREATED WITH ANTI-TNF ANTIBODIES

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Background: One of the causes of insufficient response to biological drugs is the production of anti-drug antibodies (ADA) (1). These antibodies can decrease the effectiveness of treatment by altering bioavailability or by neutralizing the drug. In addition, they may contribute to hypersensitivity reactions. Some ADA are directed against IgG allotypes, which are protein polymorphisms able to induce an immune response in incompatible subjects. Infliximab (INX) and adalimumab (ADM) have the G1m17,1 allotypes, while about 50% of the Europeans are homozygous for the incompatible G1m3,n allotypes. Therefore, the allotypes could contribute to ADA and, in this way, explain the recently described loss of efficiency of INX in allotype-incompatible RA patients (2).
Objectives: We aimed to analyze the usefulness of IgG1 allotypes as biomarker of the development of ADA against INX and ADM.
Methods: The presence of ADA was determined in 252 consecutive patients with inflammatory arthritis in the Hospital La Paz (116 with rheumatoid arthritis (RA), 74 with ankylosing spondylitis (AS), 26 with psoriatic arthritis, 17 with non-radiographic spondylitis, 11 with spondylitis and inflammatory bowel disease, 3 with uveitis and 5 with other arthropathies). Patients were assessed during INX treatment (151), or with ADM (82), or sequentially during treatment with INX and ADM (19). ADA were determined by two-site bridging ELISA as described (1). Allotypes of IgG1 were determined by genotyping 2 SNPs, rs1071803 (for allotype G1m17/G1m3) and rs11621259 (for allotype G1m1/null) with the SNaPshot Multiplex kit (Applied Biosystems) as reported (2).
Results: Patients with compatible allotypes (carriers of G1m17,1) showed a larger frequency of ADA (33% *vs.* 20%, p=0.02) and a trend toward higher titers of these antibodies ($18.0x10^3$ *vs.* $8.3x10^3$ AU, ns) than patients with incompatible allotypes (homozygous for G1m3,n). This association was clearer in patients treated with INX (41% *vs.* 25%, p=0.03) than in those treated with ADM (18% *vs.* 12%, ns). ADA were more frequent in patients treated with INX than in those treated with ADM, as already known. Multivariate analysis showed that the frequency of ADA was increased in patients with RA compared to other diseases (OR =7.6, $p<0.0001$), and decreased in older patients (OR =0.65 per 10 years, $p<0.001$). Other factors, such as sex, having AS against other diseases, and treatment with methotrexate or corticosteroids, were not associated with ADA.
Conclusions: Patients with compatible allotypes showed more frequently ADA than patients with incompatible allotypes, showing for the first time this association in patients treated with INX and reinforcing the previously reported association for ADM (3). These results suggest a genetic factor in linkage with the allotype, but different from it, that will predispose to ADA.
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Outcome measures in clinical practice in gout and CPPD. The use of the new EULAR guidelines

OP0017 MEDICATION TAKING BEHAVIOUR OF ALLOPURINOL TREATMENT AMONG PATIENTS WITH GOUT: A RETROSPECTIVE COHORT STUDY IN THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

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Background: Lowering serum uric acid concentrations is effective to control gout attack and prevent formation of tophi. Persistence with and adherence to uric acid lowering therapy are important to achieve benefit from medication. Therefore, insights into medication taking behaviour and factors influencing it, are extremely important.
Objectives: To describe patterns of persistence with and adherence to allopurinol treatment among gout patients in the UK, and explore determinants of non-persistence and non-adherence.
Methods: A retrospective cohort study using the UK Clinical Practice Research Datalink (CPRD) was conducted. Patients with a first ever diagnosing coding for gout between 1st January 1987 and 30th June 2014 were included. Start of follow-up was defined as the first prescription of allopurinol after the start of valid data collection. Patients were excluded if they were younger than 40 years, were (ever) users of febuxostat and probenecid, or had a follow-up of less than 90 days after completion of the first prescription. Determinants included patient characteristics (at baseline), medication use (6 months prior to index-date) and other comorbidities (ever before index-date). Medication taking behaviour was described by non-persistence (occurrence of a first gap of 30 or 90 days) and non-adherence (proportion of days covered [PDC] over observation period) to allopurinol treatment. Kaplan Meier survival and multivariable Cox- and logistic regression were used to estimate the median time until discontinuation, and the strength of the association between determinants with non-persistence (90-day gap) and non-adherence, respectively.
Results: A total of 47.744 gout patients (75.6% men; mean age 63.9 years) received allopurinol exclusively. After 5.3 years (SD 4.6) of follow-up 77% had a gap of 30-days and 54% had a gap of 90-days, and were non-persistence. Median survival time until discontinuation was 229 days (95% confidence interval [CI] 224 – 235) for a 30-day and 1059 days (CI 1012 – 1107) for a 90-day gap. The median PDC was 0.67 (IQR: 0.64). Over half of the patients (61%) were non-adherent ($PDC<0.80$) over the study period.
Females (HR 1.10; 95% CI 1.06–1.13; OR 1.21; CI 1.15–1.28) and current smokers (HR 1.15; CI 1.11–1.20; OR 1.17; CI 1.10–1.25) have an increased risk on non-persistence and non-adherence, while older age (ref: <50 years) (HR 0.77: CI, 0.74–0.80; OR 0.61; CI 0.58–0.65), overweight (HR 0.89; CI 0.86–0.92; OR 0.86; CI 0.82–0.91), receiving anti-hypertensive (HR 0.92; CI 0.89–0.96; OR: 0.64; CI 0.60–0.67), colchicine (OR 0.94; CI 0.89–0.98) and suffering from dementia (HR 0.58; CI 0.45–0.73; OR 0.59; CI 0.46–0.77), depression (HR 0.94; CI 0.89–0.99), diabetes (HR 0.86; CI 0.83–0.89; OR 0.90; CI 0.84–0.96) and dyslipidaemia (OR 0.81; CI 0.77–0.85) appear to decrease the risk of non-persistence and/or non-adherence.
Conclusions: This is the first large population based study in Europe which showed poor medication taking behaviour among gout patients initiating allopurinol. Females and current smokers have an increased risk, while an older age, overweight, receiving anti-hypertensives and suffering from certain comorbidities appear to decrease the risk of non-persistence and non-adherence.
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OP0018 HYPERURICEMIA INCREASES MORTALITY ONLY IN PATIENTS WITH GOUT AND EXISTING CARDIOVASCULAR DISEASE. A PROSPECTIVE ANALYSIS FROM THE BUSSELTON HEALTH STUDY

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Background: Hyperuricemia is increasingly prevalent and associated with cardiovascular disease [1]. While hyperuricemia can induce endothelial dysfunction, oxidative stress and inflammation uncertainty remains regarding the association between hyperuricemia and vascular events [2,3].
Objectives: Investigate whether baseline and/or time averaged UA levels were associated with cardiovascular events and mortality in the Busselton Health Study (BHS) cohort.
Methods: Prospective study of the BHS cohort (n=4,171), using baseline serum UA measures and 15 year follow-up [4]. Outcomes included were cardiovascular events (CVE) and mortality, derived from State-wide registries. Hazard ratios (HR) for UA level as continuous and categorical (low, medium, high) predictor of outcomes, stratified for baseline cardiovascular disease and a history of gout were analysed by multivariate Cox regression.
Results: Hyperuricemia was present in 9.4% in participants free of CVE and 16.5% in those with CVE at baseline. In those free of CVE (n=3,475), a 0.1mmol/L rise in UA level was associated with increased mortality (HR 1.19, CI 1.04–1.36), cardiovascular mortality (HR 1.27, CI 1.03–1.57) and first CVE (HR 1.28, CI 1.13–1.44) after age & sex adjustment. Hyperuricemia significantly increased the risk of a first CVE (HR 1.52, CI 1.13–2.04). However, adjustment for a range of traditional cardiovascular risk factors attenuated these associations. Results were similar for the subset of 2,139 participants using multiple UA measures over time. In the fully adjusted model, gout was a significant independent predictor of mortality only in participants with a history of CVE at baseline (HR 1.75; CI 1.04–2.95).
Conclusions: Hyperuricemia is highly prevalent in the Busselton region of Western Australia and independently increased the risk CVE or mortality events in those with existing CVE and gout. UA lowering therapy for CVE prevention is advisable for patients with a history of gout and CVE, but clearly not warranted in those with asymptomatic hyperuricemia.
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