FRI0240 CLINICAL TRIAL TO DETERMINE WHETHER ALTERING THE REGIMEN OF PEGLOTICASE ADMINISTRATION CAN INCREASE THE FREQUENCY OF SUBJECTS HAVING SUSTAINED LOWERING OF SERUM URATE

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Background: Pegloticase is a pegylated recombinant mammalian uricase approved for treatment of persons with chronic gout refractory to standard urate-lowering therapy.[1] Despite initial profound reduction of serum urate (sUA), patients may lose the urate lowering effect of pegloticase owing to the development of anti-drug antibodies.[2] As a result, only 42% of treated patients had sustained urate lowering in the registration trials, and infusion reactions (IRs) occurred in 26% receiving the biweekly dosing regimen compared to 5% of placebo-treated patients.[1] Examination of pegloticase pharmacokinetics[2] indicated that the biweekly regimen may not maintain sufficiently high levels of drug during the first 2 weeks of therapy, possibly contributing to immunogenicity.
Objectives: To determine whether an additional dose of 8 mg of pegloticase 1 week after the initial dose and 1 week before the subsequent dose might be sufficient to maintain high serum pegloticase levels and contribute to the development of high zone tolerance and a more persistent urate lowering effect. (NCT02598596)
Methods: This is a multi-centre, open-label trial enrolling patients with chronic gout whose sUA was not maintained ≤6 mg/dL. Background urate lowering therapy was discontinued and patients were treated with 3 weekly doses of 8 mg pegloticase followed by biweekly administration of 8 mg of pegloticase for a total of 10 doses over 17 weeks. After the first administration, dosing was only permitted if the sUA was ≤6 mg/dL. Standard infusion and gout flare prophylaxis were required. The primary outcome was the maintenance of sUA at ≤6 mg/dL throughout the treatment period.
Results: 50 patients have been enrolled with a mean age of 59.8±16.3 years. Of the 50 patients, 31 (62%) completed all study activities, 7 were non-compliant, 8 withdrew consent, 2 were discontinued by the PI and 2 were discontinued for an adverse event (AE). Patients have received a total of 315 infusions to date. Only 1 patient had a mild IR (0.3% of infusions) that did not meet the criteria for anaphylaxis. 38 patients reported at least 1 AE, the most common being a gout flare (52%). 8 patients (16%) reported severe AEs, including 5 with gout flares. Of the 50 evaluable patients, there were 22 responders (44%), 21 nonresponders (42%) and 7 patients were not evaluable (14%). It is notable that responders had significantly higher trough levels of pegloticase than nonresponders 1 week after the initial infusion (1.45 ug/ml, n=22 vs 1.02 ug/ml, n=21, p=0.02) that persisted throughout the trial, supporting the contention that higher levels of drug are required to promote tolerance and response.
Conclusions: The tolerization regimen of pegloticase treatment is well tolerated. Only one IR was noted as administration of pegloticase was avoided in those with a sUA >6 mg/dL. The tolerization regimen may be associated with a somewhat higher frequency of patients achieving a persistent urate lowering effect. Trough levels of pegloticase separated responders from nonresponders throughout the trial and may be useful to develop an optimal treatment regimen.

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FRI0241 THE EFFECT OF FEBUXOSTAT ON INFLAMMATORY AND CARDIOVASCULAR BIOMARKERS IN HYPERURICEMIC HYPERTENSIVE PATIENTS

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Background: Hyperuricemia (HU) is associated with hypertension (HTN) and adverse cardiovascular (CV) events. Potential mechanisms include endothelial xanthine oxidoreductase (XO) activity, direct effects of circulating soluble urate, and inflammation from crystal deposits. A phase 2 double-blind placebo (PBO)-controlled randomised trial tested the ability of 6 weeks treatment with the selective XO inhibitor febuxostat (FBX) to reduce blood pressure in hyperuricemic HTN patients who had no history of gout. A planned subgroup analysis showed reduction of systolic blood pressure (SBP) by 6.7 mmHg (95% CI 0–13.3) as assessed by 24 hour ambulatory BP measurement (ABPM) in HTN subjects with normal renal function (eGFR ≥90).[1]
Objectives: To explore mechanistic links between HU and CV disease we examined the effect of treatment with FBX on inflammatory and vascular biomarkers.
Methods: Entry criteria included ABPM SBP of ≥130 and≤165 mmHg; taking ≤2 BP drugs at baseline; and baseline serum urate (sUA) of ≥420 μM. 121 subjects were randomised 1:1 to FBX 80 mg OD or PBO for 6 weeks. Serum and whole blood mRNA samples were taken at screening (d-21), d1 pre-treatment, after 3 w and after 6 w of FBX/PBO.
Soluble markers were measured using a 50-analyte multiplex array (from Myriad RBM HuMAP panel v1.6) and included mediators previously implicated in gout and in CV associations with HU, including CCL2 (MCP-1), CXCL8 (IL-8), E- and P-selectins, cystatin C, ICAM-1, IL-6, leptin, MMPs, MPO, SerpinE1 (PAI-1), TNFα, VCAM-1 and vWF. Additional candidates (angiotensin (AT)-II, hsCRP, insulin) were measured by ELISA. RNAseq was done on the Illumina HiSeq2000 platform with 20–30 million 50 bp paired-end reads and analysed for fold change vs baseline.
Results: Serum urate was reduced by a mean of 190 μM at week 6 in FBX-treated subjects and 0 μM with PBO. Nominally significant differences in change from baseline between PBO and FBX were noted in ICAM-1 (PBO −9.5, FBX +7.0 ng/ml at w6; uncorrected p=0.006) and SerpinE1 (−4.1,+30.9; 0.004). There was no baseline association between sUA and key markers on univariate, multiple linear regression analyses, or principle component regression.
Nonparametric analysis showed marginally significant differences between FBX and PBO in the changes in CRP (unadjusted p=0.26 at w3, 0.018 w6), ICAM-1 (0.023, 0.063) and LOX-1 (0.356, 0.044). The effect of FBX was not significant for other soluble mediators including AT-II, CCL2, CRP, CXCL8, insulin, or MMPs.
Many mRNA transcripts of interest (including CXCL8, SERPINE1) showed low levels in blood and no association between fold-change and reduction in sUA. Changes in CST3, MIF, S100A8 and S100A9 expression were associated with change in sUA.
Conclusions: In these HU HTN subjects without gout no significant relationship was found between sUA and inflammatory or CV markers at baseline. FBX effects on these biomarkers are sporadic, expected when evaluating many markers in a relatively small sample. These findings do not support a direct role for soluble urate in HU-associated HTN or CV disease. Limitations include the non-gout population studied, the relatively narrow range of baseline BP, and short treatment duration.

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FRI0242 IMPAIRMENT IN THE RATES OF INCIDENCE, MORTALITY, STAYS AND ANNUAL COSTS OF HOSPITALIZATIONS FOR GOUT IN THE SPANISH NATIONAL HEALTH SYSTEM

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Background: Gout is the most common inflammatory articular disease in adults concerning a 1%–2% of the general population, and even a 4%–5% in older than 70 years. Recently, it has been reported an increase of the prevalence of gout, especially in developed countries.
Objectives: The principal purpose of our study is to describe the clinical and epidemiological characteristics of hospitalised patients with diagnosis of gout in Spain including mortality, comorbidities and healthcare costs in the last decade
Methods: Retrospective observational study based on data from the Database of Hospital from the Spanish National Health Service. The study was conducted in patients over eighteen years old with any gout diagnosis as principal or other diagnosis, who were admitted in the hospital between the years 2005–2015. The clinical characteristics analysed were sex, age, costs and length of hospital stay. Comorbidities as diabetes, congestive heart failure, acute myocardial infarction and cerebrovascular disease were identified with *International Classification of Diseases, ninth revision, common modification (*ICD-9-CM).