Background: Pegloticase is a pegylated recombinant mammalian uricase approved for treatment of persons with chronic gout refractory to standard urate-lowering therapy. 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. 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. 

Objectives: To determine whether an additional dose 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.

Methods: This is a multi-centre, open-label trial enrolling patients with chronic gout whose sUA was not <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 (0.03% 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 μg/mL, n=22 vs 1.02 μg/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.

REFERENCES:


THE EFFECT OF FEBUKOSTAT ON INFLAMMATORY AND CARDIOVASCULAR BIOMARKERS IN HYPERURICEMIC HYPERTENSION 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 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 hypertensive HTN patients who had failed histotonic BP lowering therapy. A sub-analysis showed reduction of systolic blood pressure (SBP) by 6.7 mmHg (95% CI: 0.0 – 13.3) as assessed by 24 hour ambulatory BP measurement (ABPM) in HTN subjects with normal renal function (eGFR >90). 

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 (antiangiogenic (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. Nominal significant differences in change from baseline between PBO and FBX were noted in ICAM-1 (PBO – 9.5, FBX +7.0 μg/mL at w6; uncorrected p=0.006) and SerpinE1 (p = 4.1, +30.9; 0.004). There was no baseline association between sUA and key markers on univariate, multivariable linear regression analyses, or principle component regression. Nonparametric analysis showed marginaly significant differences between FBX and PBO in the changes in CRP (unadjusted p=0.026 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 analysis and reduction in sUA. Changes in BST3, MIF, S100A8 and S100A9 expression were associated with change in sUA.

Conclusions: In these HU HTN subjects without a gout 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.

REFERENCE:


Results: The study cohort included 192,037 patients with gout, 82.6% of those were males. There was a progressive increase in the number of hospitalised patients with gout from 12,851 patients in 2005 to 23,318 in 2015; this was associated with an increase in mortality, reaching its highest value in 2015 with a 4.9% of gout hospitalised patients. The average age at death in 2015 was 79.2 years and 85.16 years in male and female respectively, an age slightly lower than in the general population. The average cost in these hospitalised patients was 4931 €. Reaching a peak of 5384 € in the last year. The hospital stay reached its lowest numbers in 2015 with an average of 8.9 days per patient. These comorbidities had a statistical association with an added mortality risk in cerebrovascular disease (odds ratio [OR] 1.57, 95% confidence interval [CI] 1.46–1.49), liver disease (OR 2.61 95% CI 2.34–2.9), kidney disease (OR 1.34 95% CI 1.28–1.41), dementia (OR 2.13 95% CI 1.88–2.42). On the contrary, in type 2 diabetes (OR 0.92 95% CI 0.87–0.96), we found a statistically significant lower mortality risk. Furthermore, it was found a statistically reduced mortality risk in females (OR 0.85 95% CI 0.87–0.88). We further aimed to analyse the efficacy and safety of anakinra in acute CPP arthritis. In contrast, the relevance of anakinra in acute CPP arthritis has not given much attention.

Methods: All patients above 18 years of age with an ICD-diagnosis of gout from Jan 2015 through Feb 2017 listed at any of twelve randomly selected primary health care centres or the rheumatology department at Sahlgrenska University hospital in the Western Sweden Health Care Region (WISHCR) were identified. They were sent a questionnaire, regarding demographics, lifestyle factors such as smoking status, alcohol consumption, physical activity, body mass index (BMI) categorised into 4 levels in the analyses) and comorbidities such as diabetes and hypertension. All responders aged 18–84 years were matched to five control individuals, without gout, by sex and age. Control individuals were selected from a random sample of 52,348 individuals aged 16–84 years who participated in the National Public Health survey in Sweden year 2015. This survey is a national study on health, lifestyle and living conditions. Alcohol consumption was categorised as none and any with/without binge drinking behaviour. Binge drinking was (liberally) defined as consuming more than four (women) or five glasses (men) on any occasion.

Conditional logistic regression models were used to compare cases and controls with regard to lifestyle factors and comorbidities. Multivariate analyses were also performed, including BMI, smoking status, alcohol consumption, and physical activity.

Results: Of the 1589 invited gout patients, 868 responded and 79.7% were male. Non-responders were more often young men. Mean age was 69.3 (std:10.5) years for men and 71.8 (std: 9.9) years for women with gout. Male gout patients were in multivariate analyses more likely to be overweight (OR 1.67 (95% CI: 1.31–2.14), obese (OR: 2.20 (95% CI: 1.64–2.94)), have binge drink behaviour (OR 3.32 (95% CI: 2.39–4.62)), and had lower levels of physical activity compared to controls (table 1). Current smoking habits did not differ between male gout patients and controls.

Female gout patients were in multivariate analyses more likely to be overweight (OR 1.87 (95% CI: 1.05–3.33)), obese (OR: 3.62 (95% CI: 1.96–6.72)), and have binge drink behaviour (OR 4.28 (95% CI: 1.92–9.53)), but did not not differ from current smoking habits or physical activity compared to controls.

In bivariate analyses, comorbidities such as diabetes and hypertension, were significantly more common in gout patients among both sexes.

Conclusions: In Spain we have a progressive increase in the hospital admissions for gout, higher mortality rates and higher healthcare costs. This shows that lifestyle factors play a significant role in developing and maintaining disease.

Disclosure of Interest: None declared


Abstract FRI0244 – Table 1. Incidence, mortality, stays and annual costs of hospitalisation for gout of the Health National System

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
<th>Mortality Number (%)</th>
<th>Average hospital stay (SD)/cost (SD)</th>
<th>Cost/year in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>12,850</td>
<td>532 (4.1%)</td>
<td>11.00/4219 542.0</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>13,163</td>
<td>479 (3.6%)</td>
<td>10.63/4269 562.6</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>13,896</td>
<td>544 (3.9%)</td>
<td>10.45/4459 61.6</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>15,292</td>
<td>601 (3.9%)</td>
<td>10.58/4838 74</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>16,172</td>
<td>630 (3.9%)</td>
<td>10.33/4997 80.8</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>16,803</td>
<td>658 (3.9%)</td>
<td>9.96/5205 87.5</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>18,482</td>
<td>781 (4.2%)</td>
<td>9.62/5385 99.5</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>19,179</td>
<td>897 (4.7%)</td>
<td>9.21/5247 100.6</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>20,777</td>
<td>968 (4.5%)</td>
<td>9.09/5166 107.3</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>22,105</td>
<td>991 (4.5%)</td>
<td>8.94/5080 112.3</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>23,318</td>
<td>1139 (4.9%)</td>
<td>8.90/5384 125.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>192,037</td>
<td>8178 (4.3%)</td>
<td>9.74/4999 959.5</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Our results suggest that anakinra could be a relevant alternative for managing acute CPP arthritis, leading to rapid relief of inflammatory symptoms, with a good tolerance.

Disclosure of Interest: None declared

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FRIO243

ANKINRA FOR CALCULUM PYROPHOSPHATE CRYSTAL ARTHRITIS: AN EFFICIENT, SAFE ALTERNATIVE TREATMENT

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Background: Calcium pyrophosphate (CPP) deposition is a frequent joint disease with increased prevalence in older people in whom treatment of acute CPP arthritis with conventional therapies such as colchicine, corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) could be contraindicated or not used at an optimal dose. As recommended in gout, anakinra might represent an alternative treatment for acute arthritis. In contrast, the relevance of anakinra in acute CPP arthritis has not given much attention.

Objectives: We further aimed to analyse the efficacy and safety of anakinra in acute CPP arthritis in a large cohort.

Methods: We retrospectively included all patients receiving anakinra for acute CPP arthritis between January 2011 and 2017. Medical history data were collected including hypertension, diabetes mellitus, cardiovascular disease, history of gastrointestinal ulcer, renal impairment and comorbid treatments including anticoagulants or antiplatelet drugs. The following data were collected before and 4 days after the first anakinra injection: swollen joint count (SJC), tender joint count (TJC), pain score on a visual analogue scale (VAS, 0–100 mm) and C-reactive protein (CRP) level. A good response was defined according the evaluation of the physician or documentation in the chart of the phrase “good response” after anakinra treatment.

Results: We included 33 patients (24 women; mean age 79.2±12.8 years). Mean duration of acute arthritis 10.2±12.9 days. CPP arthritis was confirmed by the presence of CCP crystals in synovial fluid in 28/33 (84.8%) patients. For the remaining 5 patients, the diagnosis was confirmed by CPP deposition features seen on imaging. Corticosteroids, NSAIDs and colchicine were previous treatments, without significant improvement in 12 (36.4%), 7 (21.2%) and 18 (54.5%) patients, respectively. The mean dose of corticosteroids was 20.8±8.2 mg/day. Among the 33 patients, 32 had a documented visit at day 4. The number of good responders was 27 (81.8%). At day 4, patients showed decreased mean VAS pain score (from 64.8±26.5 to 21.2±19.7 mm, p<0.0001), TJC (3.9±2.7 to 0.9±1.0, p<0.0001) and CRP level (116.1±71.6 to 26.0±23.1 mg/L, p<0.0001). Anakinra was well tolerated. Only one patient had pneumonitis that was resolved with oral antibacterial agents.

Conclusions: Compared to the general population, patients with gout were more often obese (in particular women) and had higher occurrence of binge drinking behaviour (in particular men). The lower level of physical activity (men) and normal frequency of smoking among gout patients may be a consequence of the high comorbidity rates.