TREATMENT WITH PEGLOTICASE IMPROVES HEPATIC FIBROSIS ESTIMATED BY FIBROSIS-4 INDEX IN SUBJECTS WITH CHRONIC REFRACTORY GOUT

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Background: Hyperuricemia is associated with non-alcoholic fatty liver disease (NAFLD)1,2, but the relationship to fibrosis remains uncertain3. Moreover, it is not known whether lowering serum urate will affect the course of NAFLD. The availability of data from two randomized trials of pegloticase, a pegylated recombinant mammalian uricase, that profoundly decreases serum urate afforded the opportunity to test the hypothesis that lowering urate might improve NAFLD.

Objectives: To determine whether treatment of chronic refractory gout patients with pegloticase was associated with improvement in NAFLD determined by Fibrosis 4 index (Fib4).

Methods: Databases from patients with chronic refractory gout who participated in two randomized 6 month clinical trials (RCTs) of pegloticase were analyzed4. Sub-sets who had persistent urate lowering to levels <1 mg/dL in response to biweekly pegloticase (Responders, n=36) were compared to those who received placebo (n=43). Since liver biopsy information was not available on these subjects, we relied on Fib4, a validated non-invasive estimate of liver fibrosis in a placebo (n=43). Since liver biopsy information was not available on these sub-sets, we relied on Fib4, a validated non-invasive estimate of liver fibrosis in a variety of liver diseases5-10 calculated from measurements of AST, ALT, platelet count and age (Age x AST/platelets x x ALT). A Fib4 value of 1.3 is an indication that further evaluation of liver disease is warranted. Any patients treated with pegloticase who had a Fib4 value > 1.3 were considered to have persistent liver disease.

Results: At baseline, the mean Fib4 values were 1.40 ± 0.86 in pegloticase responders and 1.04 ± 0.53 in subjects receiving placebo. As shown in figure 1, subjects receiving placebo exhibited a change of 0.26 ± 0.41 in the Fib4 score over the six months of the RCTs compared to 0.13 ± 0.62 in the pegloticase responders (p<0.048; by linear regression). When only the subjects with a Fib4 value > 1.3 were considered, a significant difference in the change in the Fib4 values over the 6 months of the trial between pegloticase responders and those receiving placebo was also observed (p=0.35 x 0.67 vs 0.37 ± 0.42, p=0.004, by linear regression). The correlations between serum urate area under the curve (AUC) over the 6 months of the trial and the change in Fib4 value was r=0.33, p=0.00004 (Spearman rank-order correlation coefficient). Finally, multiple linear regression analysis indicated serum urate AUC (as a surrogate measure for group) is the main contributor to the change in Fib4 (p=0.018 by linear regression).

Conclusion: The data are consistent with the conclusion that persistent lowering of serum urate had a significant impact on Fib4 levels, implying a possible effect on the course of NAFLD. The results support a more complete analysis involving biopsy examination of the impact of urate on liver inflammation and fibrosis.

References:

Disclosure of Interests: : Naomi Schlesinger Grant/research support from: Pfizer, Amgen, Consultant of: Novartis, Horizon Therapeutics, Selecta Bio- sciences, Olatec, IFM Therapeutics, Mallinckrodt Pharmaceuticals, Anthony Yeo Employee of: Horizon Therapeutics, Peter Lipsky Consultant of: Horizon Therapeutics

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THU0434 LEFLUNOMIDE CO-THERAPY WITH PEGLOTICASE IN UNCONTROLLED GOUT

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Background: Pegloticase is a PEGylated biologic for uncontrolled gout that has well-established efficacy. However, anti-drug antibody (ADA) development causes many patients to discontinue treatment before receiving the full therapeutic course.1 ADAs bind to the pegloticase molecule, leading to reduced therapeu- tic efficacy and discontinuation of therapy.2 Emerging data indicates that co-treatment with pegloticase and immunomodulating agents may prevent ADA development, allowing more patients to receive a full course of treatment. Prior case reports describe the results of pegloticase treatment with methotrexate, azathioprine or cyclosporine3,4; however, the literature does not contain information on the use of leflunomide with pegloticase.

Objectives: To evaluate overall pegloticase responder rate in uncontrolled gout patients co-treated with leflunomide.

Methods: This retrospective study was conducted in a rheumatology practice where an immunomodulatory agent is typically used in conjunction with peg- loticase. Patients co-treated with oral leflunomide (20mg/day) and pegloticase (8mg infusion) were included. Extracted data included demographics, gout characteris- tics, pegloticase therapy parameters (serum uric acid [sUA], number of infusions), leflunomide therapy parameters (timing with respect to the first pegloticase infu- sion, dose, route), adverse events (e.g., gout flare, infusion reactions), and safety information (clinical laboratory parameters). Prior to each infusion all patients were administered a standard prophylaxis regimen of fexofenadine the night before and day of infusion, sulomedrol day of infusion. The primary outcome was the propor- tion of pegloticase responders, defined as those receiving ≥12 infusions.

Results: At data collection, 10 patients (5 male, 7.2 ± 12.5 years old, baseline sUA = 6.59 ± 3.15 mg/dL) had been co-treated with pegloticase and leflunomide. 4 patients (40%) received ≥12 infusions of pegloticase; 2 patients began treat- ment but were lost to follow-up, though neither of these patients experienced a rise in sUA during therapy. Of the 6 patients described, 4 met the primary outcome for a responder and 2 were lost to follow-up, resulting in 4/6 or 66% completion rate. No new safety concerns emerged. One patient had 3 gout flares during treatment and 1 patient required emergency care because of loss of con- sciousness and woonizor prior to pegloticase infusion due to pre-medication with sulomedrol. No clinically meaningful laboratory value changes occurred, with the exception of a mild and transient ALT rise in 1 patient.

Conclusion: Preliminary evidence suggests that low-to-moderate immunomodulation can minimize or prevent ADA formation against pegloticase and increase the number of patients fully benefiting from pegloticase. No prior studies have examined the effect of leflunomide on pegloticase responder rates. The current study indicates that oral leflunomide may be a viable immunomodulator for patients with uncontrolled gout undergoing pegloticase therapy. The current study indicates that oral leflunomide may be a viable immunomodulator for patients with uncontrolled gout undergoing pegloticase therapy.

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Background: Chondrocalcinosis is a painful rheumatic condition caused by the deposition of calcium pyrophosphate dihydrate crystals (CPPD) in joint tissues, and especially in cartilage. It is known that CPPD crystals cause inflammation and degenerative changes in joint, but the underlying mechanisms remain poorly understood. In particular, nothing is known about how these crystals regulate transmembrane heparan sulphate proteoglycans (HSPGs). Our attention focused on one family of HSPGs called syndecans as they have important roles both as adhesion molecules, by mediating chondrocyte-extracellular matrix interactions, and as modulators of intracellular signaling triggered by cytokines and growth factors.

Objectives: The aim of this study was to evaluate how CPPD crystals modulates syndecan expression in chondrocytes and in cartilage, and how this modulation can be ultimately linked to cartilage damage during chondrocalcinosis.

Methods: Murine chondrocytic ATDC5 cells were stimulated with 0,1mg/ml CPPD crystals or with 0,1mg/ml basic-calcium phosphate crystals (BCP), a family of calcium-containing crystals found in other rheumatic conditions such as osteoarthritis (OA). Cytotoxicity was evaluated by lactate dehydrogenase (LDH) release in the supernatant at 30 minutes, and 3, 6, 24 hours after stimulation. At the same time-points, mRNA expression levels of syndecans (Synd-1, -2, -3, -4) and of matrix-degrading enzymes (Mmp-3, -9, -13; Adamts-4, -5) was analysed by qRT-PCR. Finally, Syndecan-4 protein expression was studied by immunohistochemistry (IHC) in cartilage samples of patients with chondrocalcinosis and in samples of patients with severe OA without chondrocalcinosis as control.

Results: LDH assay revealed no increased cytotoxicity by CPPD or BCP at any time-point. qRT-PCR indicated that CPPD crystals but not BCP crystals induced Synd-2 and -3 upregulation at 30 minutes after stimulation and Synd-4 upregulation at 3 hours, while no modulation of syndecans was seen at later time-points. CPPD also induced Adams-4 expression at 3 hours after stimulation, and Mmp-9 expression at 3 and 6 hours. The expression of the other matrix-degrading enzymes was not affected. Human chondrocalcinosis cartilage exhibited enhanced Synd-4 expression compared to severe OA cartilage containing BCP calcification. Interestingly, Synd-4 expression was observed in the extracellular matrix but not on cell membrane, suggesting that maybe Synd-4 undergoes shedding (Figure 1).

Conclusion: BCP and CPPD crystals seem to trigger differential effects in terms of modulation of syndecans in chondrocytic cells. CPPD crystals induce Synd-4 and Adams-4 and Mmp-9 which are not induced by BCP crystals. It remains to be clarified whether the two events are interlinked. In particular, further studies are required to investigate if Adams-4 and Mmp-9 are involved in Synd-4 shedding or if vice versa Synd-4 regulates Adams-4 and Mmp-9 activation and downstream cartilage breakdown.

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ASSESSMENT OF CARdiovasculAr RISK LEVELS IN CPPD Versus RA And Gout, AND RISK-FLuctuation ANALysis BASED ON CALCulator TYPE: ATP III and REYNOLDS RISK SCORE

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Background: Cardiovascular risk in CPPD patients is not so well evaluated as in other rheumatic diseases, and optimal risk calculators for patients with calcium pyrophosphate crystal deposition disease have not yet been studied.

Objectives: To assess CVR and compare stratification results using ATP III and Reynolds Risk Score (RRS) calculators in CPPD, RA and gout patients versus the control subjects.

Methods: The case-control study included 168 patients aged 18 - 80 years old, with 42 participants in each subgroup - CPPD, gout, RA patients and healthy volunteers, matched by gender (10 males and 32 females) and age (mean age 54 years). CPPD diagnosis was based on McCarty 1961 y criteria, RA – following ACR/EULAR 2010 y criteria, and gout - ACR/EULAR 2015 criteria. CPPD and gout diagnosis was crystal- verified in all cases. Exclusion criteria were as follows: diabetes mellitus and eGFR<60 ml/min/1.73m². The following data was collected for all patients: anthropometric parameters, BP, lab tests, including serum glucose level, creatinine, total cholesterol (TC), HDLp, CRP; CVR was assessed using ATP III and RRS scales. Statistica 12.0 package was used for statistical data processing.

Results: Both groups were comparable in terms of anthropometric parameters, rates of individual indicators and factors did not differ, except for family history of cardiovascular disease, systolic BP, HDLp, hsCRP (see Table).

Table 1. Risk factors and CVR stratification by ATP III and RRS in CPPD, RA, gout and control group.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>ATP III</th>
<th>RRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>*p&lt;0.05</td>
<td>*p&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>*p&lt;0.01</td>
<td>*p&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>*p&lt;0.01</td>
<td>*p&lt;0.01</td>
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<tr>
<td>Smoking</td>
<td>*p&lt;0.05</td>
<td>*p&lt;0.01</td>
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Based on ATP III risk calculation the number of CPPD patients with high and very high CVR was significantly higher in CPPD (9%, 12%) compared to RA (9%, 11%) and gout (9%, 7%) and the control group (8%, 9%). Mean CRP levels and number of pts with CRP ≥5mg/l were significantly lower in CPPD and control group pts, than in RA and gout, however CRP ≥5mg/l were almost similarly in all groups (43%) and only in 7% of pts from the control group (p<0.05).

Although CVR calculations based on RRS scale yielded similar results, and all groups remained comparable, nevertheless, the number of pts with high and very high CVR increased in each group, except for the control. There were no meaningful differences in the groups in TC levels, however HDLp was significantly higher in CPPD pts (p<0.05), than in RA and gout, and in the control group pts vs RA pts (p<0.05).

Conclusion: CPPD associated cardiovascular risk is considerably high and comparable to CVR levels in RA and gout. Given that RRS based CVR calculation resulted in increased number of patients with high and very high risks in all groups, except for the control group, it can be suggested that use of calculators including CRP is appropriate not only in RA pts, but also in microcrystal deposition arthropathies, associated with inflammation, therefore prospective studies on larger samples are deemed necessary.

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THU0437

SPECIFIC COMORBIDITIES ENHANCE MONOSODIUM URATE CRYSTAL DEPOSITION IN GOUT: A MULTICENTRE DUAL-ENERGY COMPUTED TOMOGRAPHY STUDY


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Background: The reasons explaining why some patients exhibit higher monosodium urate (MSU) crystal burdens than others remain largely unknown. While MSU crystal formation is enhanced by certain factors in vitro such as pH, temperature, and other ion concentrations, it is currently unknown whether comorbidities and clinical features are associated with increased MSU deposition in vivo.

Objectives: To determine which factors are associated with the burden of MSU crystal deposition quantified by dual-energy CT (DECT) in urate lowering therapy (ULT)-naive gout patients.

Methods: In this multicenter cross-sectional study, DECT scans of knees and feet were prospectively obtained from ULT-naive, or not taking any ULT for more than a year, gout patients. Demographic, clinical (including gout...