MODULATION OF THE URICOSURIC EFFECT OF FENOFIBRATE BY UGT2B7 A-327G

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RESULTS

ABSTRACT

Statement of Purpose, Innovation or Hypothesis:

Studies link elevated serum uric acid levels with gout, hypertension, diabetes, kidney and cardiovascular disease. Fenofibrate lowers serum uric acid and favorably affects lipids however identifying optimal candidates for fenofibrate remains unclear. We identified UGT2B7A-327G (rs7662029) affects fenofibrate’s disposition and lipid response and thus sought to examine its impact on its uricosuric effect within the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study.

RESULTS

Data and Results: Of the 861 participants (51% male) with a mean (SD) age of 49 (16) years, 27% were found to be A/A, 50% A/G and 23% G/G for the UGT2B7 A-327G SNP. Overall, serum uric acid was lowered by mean (SD) of 20.8% (12.8) with higher serum trough concentrations of fenofibric acid associated with greater % change in uric acid (p=0.047, p<0.0001). UGT2B7 A-327G had no significant effect on pre-fenofibrate uric acid (p=0.05). Mixed model analysis identified a significant effect of UGT2B7 A-327G on % change in uric acid for G/G (p=0.0038) and G/A (p=0.009) relative to A/A but not between G/G and G/A and therefore a recessive model combining A/G and G/G as GX was used. There was a significant difference between UGT2B7 genotypes for A/G and G/G, -19% (SE=0.91) and -22% (SE=0.51) respectively (p=0.0019).

Figure 1: Average change (mean ± se) in uric acid after 21 days of fenofibrate treatment. Pre-FA = before fenofibrate acid treatment, Post = after fenofibrate treatment.

Figure 2: Percent change in uric acid according to SLC2A9 SNP (rs734553). No significant (NS) difference by multivariate regression (see METHODS for covariates).

Figure 3: Percent change of uric acid according to UGT2B7 A-327G. AA = AA genotype, GX = GA or GG genotype.

Table 1: Study population characteristics (All Participants n=812)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Age (years)</th>
<th>Sex (male) (%)</th>
<th>BMI (kg/m²)</th>
<th>Creatinine Clearance (estim)</th>
<th>Diabetes type II (%)</th>
<th>Metabolic syndrome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>48.6 ± 18.3</td>
<td>50.0</td>
<td>28.4 ± 16.5</td>
<td>97.6 ± 30.26</td>
<td>45.0</td>
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</tr>
</tbody>
</table>

Table 2: Frequencies for SLC2A9 SNP (rs734553) and UGT2B7 A-327G (rs7662029) genotypes

<table>
<thead>
<tr>
<th>SNP</th>
<th>Number/ Genotype</th>
<th>Prevalence</th>
<th>G/G</th>
<th>G/T</th>
<th>T/T</th>
<th>A/A</th>
<th>A/G</th>
<th>A/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC2A9 SNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td></td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/T</td>
<td></td>
<td>38%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td></td>
<td>56%</td>
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</table>

CONCLUSION

• Fenofibrate’s uricosuric response variability appear to be modulated through UGT2B7 A-327G in a manner consistent with (albeit not completely explained) by serum fenofibric acid levels.21

SIGNIFICANCE

• Genetic sources of response variation to the lipid-lowering effects of fenofibrate may overlap with the uricosuric (uric acid) effects of fenofibrate and thus may contribute to clinical decision making when both dyslipidemia and hyperuricemia co-exist.

LIMITATIONS

• GOLDN study subjects were, for the most part, not hyperuricemic, all Caucasian and exposed to only 21 days of fenofibrate.

• Other genes/SNPs affecting response to fenofibrate have yet to be explored

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REFERENCES
