Exploring the mechanism of uric acid lowering effect of iguratimod

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Iguratimod (IGU) is a disease-modifying antirheumatic drug, whose activity is mainly ascribed to the inhibition of NF-κB pathway. Interestingly, we have noticed that the serum uric acid (UA) levels were decreased in 22% of rheumatoid arthritis patients taking IGU. Since there have been no reports of IGU affecting UA, we decided to explore how IGU lowers the serum UA level.

We first examined whether IGU inhibits the xanthine oxidase (XO) activity. Xanthine and XO were incubated with the drug and the production of UA was measured by absorbance at 290 nm. UA production was not inhibited by IGU. Next, we examined whether IGU or its metabolites inhibit the UA transporters. As M3 and M4 are the major metabolites in the urine, we examined the inhibitory activities of IGU and these metabolites against the major UA transporters, GLUT9 and URAT1, in the xenopus oocytes expression system. IGU and M4 inhibited the URAT1, and their IC₅₀s were 12.61 ± 0.97 μM and 120.07 ± 26.69 μM, respectively. However, the estimated maximal concentrations of these compounds in the proximal tubule were 4 - 7 times lower than the IC₅₀.

In conclusion, UA lowering effect of IGU is not likely to be explained by its or its metabolite's direct interaction with XO, URAT1, or GLUT9.