CORRESPONDENCE

Effects of Rosiglitazone on Methionine-Choline Deficient Diet–Induced Nonalcoholic Steatohepatitis

To the Editor:

We read with great interest the article by Garcia-Ruiz et al.,[1] a study which evaluated the effects of rosiglitazone on liver histology and mitochondrial function in ob/ob mice, a model of nonalcoholic fatty liver disease (NAFLD). Briefly, in this controlled study, ob/ob mice were treated at 6 weeks of age with 1 mg/kg/day rosiglitazone by mouth for 12 weeks. Garcia-Ruiz et al. evaluated the effects of rosiglitazone on liver histology and mitochondrial function in the model. They revealed that rosiglitazone treatment improved neither the NAFLD inflammatory activity nor the mitochondrial injury of the model. On the contrary, the drug increased liver steatosis, particularly microvesicular steatosis and oxidative stress compared to control groups.

To the best of our knowledge, we presented the first data concerning the effects of rosiglitazone on a nonalcoholic steatohepatitis (NASH) model induced by methionine-choline deficient diet (MCDD).[2,3] We examined the effects of 4 mg/kg/day rosiglitazone given by gavage on histological characteristics of liver in male Wistar rats at 4 and 12 weeks after commencing of feeding either with MCDD or MCDD supplied with methionine and choline (Harlan Teklad Biomedicals, Madison, WI). For grading and staging the histological lesions, the modification system of Brunt et al. was used.[4]

All MCDD-fed rats exhibited characteristics of NASH with histological evidence of both significant hepatic steatosis and inflammation. In both study periods, MCDD alone led to grade III liver steatosis, irrespective of rosiglitazone use. Rosiglitazone treatment did not change MCDD-induced liver steatosis in either study terms. The rosiglitazone treatment reduced the number of median inflammatory foci and total inflammatory cells in the MCDD + rosiglitazone group as compared to the MCDD group. Rosiglitazone therapy decreased the liver inflammation on the MCDD-induced NASH model with overt inflammation in both study terms.[2,3]

As shown in Garcia-Ruiz et al., we also observed that rosiglitazone appeared to have increased the liver malondialdehyde, luminol, and lucigenin levels; however, these differences were not statistically significant in our studies.[2,3] After cytokine tests, we observed that rosiglitazone also improved interleukin-6 levels in the 4-week study and interleukin-1β, interleukin-6, and tumor necrosis factor-α levels in the 12-week study ($P < 0.01$).[3]

Our data are the first to show the anti-inflammatory effects of rosiglitazone in NASH. We speculated that rosiglitazone's effect on cytokines may be a key mechanism of its anti-inflammatory effect in NASH.

Different NAFLD models may have different responses in terms of severity. Young ob/ob mice have been known to have fatty livers without overt histological or biological evidence of hepatic inflammation (that is, steatohepatitis).[5] Obese ob/ob mice with fatty liver and obvious steatohepatitis have been developed when challenged with lipopolysaccharide endotoxin,[6] ischemia-reperfusion, or ethanol.[7] Because we used an overt NASH model, we might have observed an anti-inflammatory role of rosiglitazone. Differences between our results and that of Garcia-Ruiz et al. may also be due to the different pathogenetic pathways of the NAFLD models.

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Potential conflict of interest: Nothing to report.

Reply:

We thank Dr. Tahan and colleagues for their interest in our article describing the effects of rosiglitazone (RGZ) on ob/ob mice with nonalcoholic steatohepatitis (NASH).[1] In these animals, we found that RGZ increases liver triglyceride concentration, serum levels of aminotransferases, liver steatosis, particularly microvesicular steatosis, oxidative stress, and impairs the activity of complex I of the mitochondrial respiratory chain (MRC). In contrast to these effects, Tahan et al. found in a rat model of NASH that RGZ attenuates liver inflammation and decreases proinflammatory cytokines, but increases markers of oxidative stress and does not change liver steatosis.[2,3] We do not have a definitive explanation for these partially divergent responses to RGZ treatment in both studies. However, there are a number of differences in the methodology that might justify, at least in part, these conflicting results. Hence, animals (rats versus mice), NASH model (diet versus leptin deficiency), and doses (4 mg/kg body weight versus 1 mg/kg body weight) were different in both studies. Difference in the animal species used in these experiments is of particular interest because variation in drug metabolism among species and even individuals may account for dissimilar response to this drug. In this respect, as Drs. Caldwell and Argo point out in their editorial,[4] polymorphisms or interspecies and intraspecies variations in the expression and tissue distribution of peroxisome proliferator-activated receptor γ might offer an explanation for the partially divergent hepatic response to RGZ in humans, rats, and mice.

The major divergences between our results and those found by Tahan et al. concern the anti-inflammatory effect of RGZ they described in their abstracts. Although in our article, we have not included the effect of RGZ on the liver concentration of proinflammatory cytokines, we found that this drug decreased the levels of tumor necrosis factor-α in liver tissue from 2.13 ± 0.19 pg/μg protein in ob/ob mice to 0.38 ± 0.02 pg/μg protein in RGZ-treated ob/ob mice (lean mice,