CORRESPONDENCE

Givosiran for Acute Intermittent Porphyria

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TO THE EDITOR: In their article on a phase 3 trial of givosiran for the treatment of acute intermittent porphyria, Balwani et al. (June 11 issue)[1] indicate that the drug may increase levels of serum creatinine. Although this side effect was considered to be an early and mostly transient event, the treatment of two patients was interrupted because chronic kidney disease (CKD) developed during the open-label extension period, a finding that emphasizes the need to identify risk factors, molecular mechanisms, and potential long-term consequences.[2] Potential confounders include the spontaneous development of CKD[3] and underlying compromised kidney function in patients with acute intermittent porphyria.

In the trial by Balwani et al., five patients who received givosiran and who had either the development or worsening of CKD had a decrease in the estimated glomerular filtration rate (eGFR) between screening and trial initiation (≤2 months), with a median reduction of 5.0 ml per minute per 1.73 m^2 of body-surface area (a decrease of 8.7%, or a median decrease of at least 2.5 ml per minute per 1.73 m^2 per month) (Fig. 1). In three of these five patients, the eGFR further decreased after trial initiation, and the eGFR values had not returned to baseline at 6 months and were not shown to be reversible.

Givosiran, which targets messenger RNA in the gene encoding delta-aminolevulinic acid synthase 1 (*ALAS1*), may accumulate in kidney tubules,[2] which are very rich in mitochondria, thereby leading to suboptimal ALAS1 levels. In rodents, such changes have led to decreased mitochondrial function in some organs[4] and to decreased *Alas1* expression during kidney injury.[5] Areas for future research could include eGFR measurement to exclude a functional effect on tubular creatinine transport and an assessment of the consequences of ALAS1 deficiency in kidney tubules under stress conditions that are similar to those in patients with acute intermittent porphyria because of underlying CKD and iron overload.

1. Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. N Engl J Med 2020;382:2289-301.
2. Assessment report: Giviaari (givosiran). European Medicines Agency, January 30, 2020 (https://www.ema.europa.eu/en/documents/assessment-report/givlaari-epar-public-assessment-report_en.pdf).
3. Pallet N, Karras A, Thervet E, Gouya L, Karim Z, Puy H. Porphyria and kidney diseases. Clin Kidney J 2018;11:191-7.
4. Saitoh S, Okano S, Nohara H, et al. 5-aminolevulinic acid (ALA) deficiency causes impaired glucose tolerance and insulin resistance coincident with an attenuation of mitochondrial function in aged mice. PLoS One 2018;13(1):e0189593.
5. Yamaoka M, Shimizu H, Takahashi T, Omori E, Morimatsu H. Dynamic changes in Bach1 expression in the kidney of rhabdomyolysis-associated acute kidney injury. PLoS One 2017;12(7):e0180934.

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THE AUTHORS REPLY: Regarding the potential effects of givosiran on kidney function, givosiran is targeted to liver by conjugation to *N*-acetylgalactosamine ligands that bind to asialoglycoprotein receptors, which are found predominantly on hepatocytes.[1,2] Consistent with this mechanism, the maximal level of givosiran at pharmacologic doses in the kidneys was approximately 10% of that in liver after subcutaneous administration in preclinical studies. Exaggerated dosing in rodents showed that givosiran had no effect on *ALAS1* mRNA expression in the kidney (see Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Renal biopsy samples obtained from two patients with worsening CKD in our trial were not consis-

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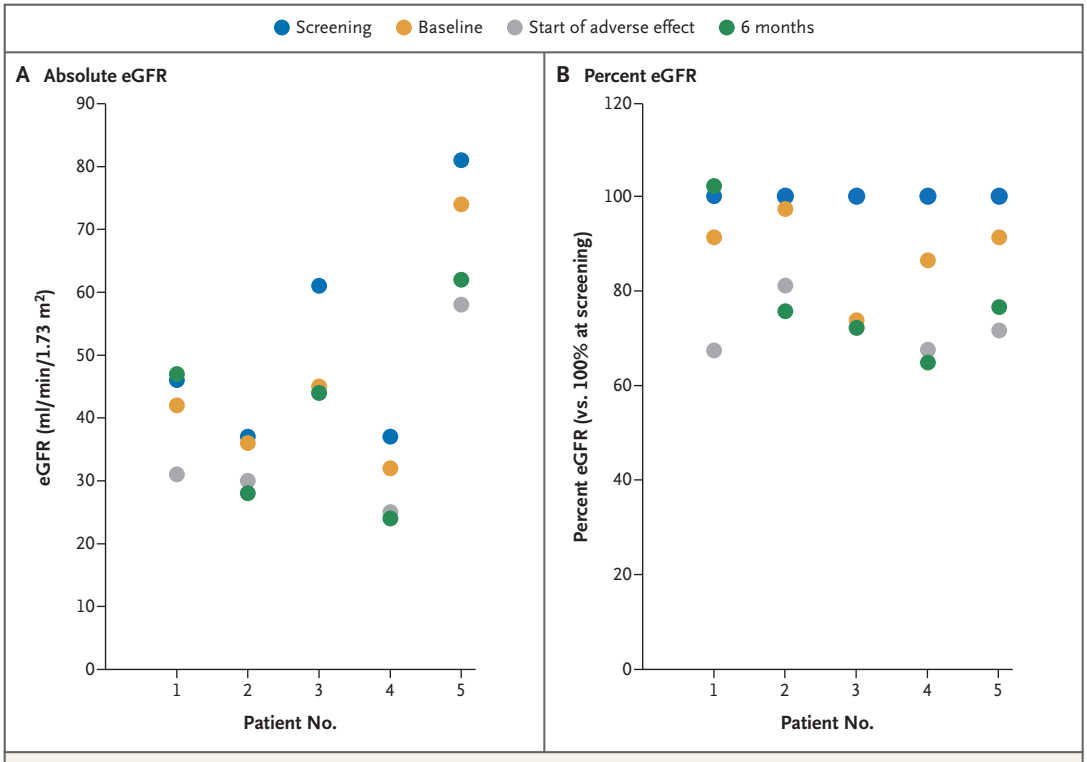

Figure 1. Changes in the Estimated Glomerular Filtration Rate (eGFR) in Five Patients with Adverse Events of Chronic Kidney Disease While Receiving Givosiran.

Panel A shows the absolute eGFR values among the five patients at screening, at baseline (trial initiation), at the beginning of the adverse event, and at 6 months. Panel B shows the eGFR at each time point in the trial as expressed as the percentage of the eGFR at screening, which was considered to be 100%. At some time points, the data points are superimposed. The data in this figure were adapted from Table S7 in the Supplementary Appendix accompanying the article by Balwani et al., available at NEJM.org.

tent with a drug-induced process[3] but rather with the patients' underlying disease. Treatment with givosiran was associated with small increases in creatinine (0.07 mg per deciliter at 3 months) in the overall trial population, changes that were mainly reversible. Some patients with preexisting renal disease had reductions in renal function that stabilized with ongoing administration of givosiran. However, consistent with labeling, monitoring of renal function during givosiran treatment is recommended as clinically indicated.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Willoughby JLS, Chan A, Sehgal A, et al. Evaluation of GalNAc-siRNA conjugate activity in pre-clinical animal models with reduced asialoglycoprotein receptor expression. Mol Ther 2018;26:105-14.
2. ASGR1 asialoglycoprotein receptor 1. Bethesda, MD: National Center for Biotechnology Information, 2020 (https://www.ncbi.nlm.nih.gov/gene/432).
3. Lee DW, Faubel S, Edelstein CL. Cytokines in acute kidney injury (AKI). Clin Nephrol 2011;76:165-73.

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RAAS Inhibitors and Risk of Covid-19

TO THE EDITOR: In a population-based case–control study conducted in Lombardy, Italy, Mancia et al. (June 18 issue)[1] found a significant association between the use of oral anticoagulant agents and coronavirus disease 2019 (Covid-19). The odds ratio for Covid-19 associated with use of