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subsequently entered into a collaboration agreement with Boehringer Ingelheim to explore the technology in immune modulation.

REFERENCES

TAMEing ADPKD with metformin: safe and effective?

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The biguanide metformin has been safely and widely used in the treatment of type 2 diabetes mellitus for decades. Preclinical studies have suggested that it may have a role in slowing disease progression in autosomal dominant polycystic kidney disease. In this issue, Perrone et al. report results from the Trial of Administration of Metformin in PKD (TAME PKD) study, a phase 2 randomized controlled trial investigating the safety and tolerability of metformin in patients in the early stages of autosomal dominant polycystic kidney disease. We discuss the implications of these findings and how they relate to a major phase 3 trial in autosomal dominant polycystic kidney disease that will start later in 2021.


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Metformin (dimethyl-biguanide) is the most commonly used oral hypoglycemic agent in the management of type 2 diabetes mellitus worldwide. Derived from guanidine, a chemical first identified from the plant Galega officinalis, an herbal remedy found to lower blood glucose in humans, it was first synthesised in the 1920s and has since gained widespread acceptance based on its effectiveness, safety, and cost. Metformin is not metabolized in humans and is excreted solely through the kidney. Common side effects include gastrointestinal symptoms such as nausea, loss of appetite, abdominal cramps, and occasional vomiting. A rare but serious adverse event is lactic acidosis. This side effect is especially seen in subjects with reduced renal elimination due to low glomerular filtration rate (GFR) and has led to the general safety recommendation that it should not be prescribed in patients with an estimated glomerular filtration rate (eGFR) of $<30$ ml/min per 1.73 m$^2$. In cases of vomiting, diarrhea or other causes of dehydration, metformin should be temporarily withdrawn.

The major mechanism of action of metformin on hepatic glucose production is still debated: There is experimental evidence both for an effect on the cytosolic redox state (inhibiting the redox shuttle enzyme mitochondrial glycerol 3-phosphate dehydrogenase) and on the activation of adenosine monophosphate (AMP) kinase (AMPK). A major energy sensor within the cell, at therapeutic concentrations ($\mu$M). Earlier observations of a direct effect on oxidative phosphorylation (mitochondrial complex 1) have since been attributed to the supra-pharmacological doses (mM) used in these studies; blood therapeutic levels in humans are $\sim10–40\mu$M. An effect of metformin on renal gluconeogenesis has not been established.

The beneficial effect of metformin on autosomal dominant polycystic kidney disease (ADPKD) was first suggested by a study by Takiar et al., who reported a reduction of cystic disease by high-dose metformin (300 mg/kg/d i.p.) in 2 severe neonatal Pkd1 mouse models including a tamoxifen-inducible Pkd1floxed conditional knockout (KO) model. Tamoxifen was given at days 9 and 10 after birth, leading to rapidly progressive cystic disease within 1 to 2 weeks. A later study in a zebrafish pkd2 morphant confirmed similar effects of metformin (2.5–20 mM) on pronephric cyst expansion by inhibiting cell proliferation but also demonstrated additional positive effects on leukocyte infiltration and autophagy. Metformin was shown to activate AMPK as
performed with metformin (300 mg/kg/d oral) in a tamoxifen-inducible condition Pkd1del conditional KO mouse model was surprisingly neutral after 3 months of treatment. One obvious difference between this study and the study by Takiar et al. was that Leonhard et al. gave tamoxifen at days 18 and 19 after birth, which leads to more slowly progressive disease, with end-stage renal failure occurring at a median age of 4 months. Thus, the beneficial effect of metformin could depend on the rate of disease progression, with greater efficacy in more rapidly progressive disease. Another difference between the 2 studies could lie in the method of drug administration. At first glance, both studies used the same dose, i.e., 300 mg/kg/d. However, in the study by Takiar et al., metformin was given i.p. whereas in the study by Leonhard et al., this was administered orally in drinking water. The oral bioavailability of metformin is 40%–60%, so the neutral study by Leonhard et al. is likely to have provided only one-half of the dose of that by Takiar et al. Importantly, the oral dose of 300 mg/kg/d in mice corresponds approximately to an oral dose of 25 mg/kg/d in humans, i.e., for a subject of 80 kg, this is equivalent to 2000 mg/d. The difference in efficacy between the 2 experimental studies could, therefore, also relate to differences in serum metformin levels. Therefore, it might be important for clinical studies to pursue the highest tolerated dose of 2000 mg/d. Differences in efficacy related to dosage is not a new issue in ADPKD, having been invoked as a possible explanation for positive, high-dose experimental studies versus neutral, lower-dose clinical trials with mTOR inhibitors. These early promising preclinical results formed the basis for the Trial of Administration of Metformin in PKD (TAME PKD) study, a phase 2 double-blind placebo-controlled randomized controlled trial investigating the safety and tolerability of metformin in patients in the early stages of ADPKD (eGFR > 60 ml/min per 1.73 m²) which began in 2016. Ninety-seven patients with ADPKD between 18–60 years of age at 2 academic centers were randomised in a 1:1 ratio to receive metformin (1000 mg twice daily) or a placebo over a period of 24 months. The patients recruited had a mean age of 42 years and a relatively high mean eGFR at entry of 86 ml/min per 1.73 m² in both groups, suggesting more slowly progressive disease overall. There were more females (78% vs. 67%) and PKD1 patients (78.7% vs. 60.9%) in the metformin group but patients in the placebo group had a greater mean height-adjusted total kidney volume (htTKV; 751 ml/m vs. 626 ml/m). Only half of the patients could be classified as falling into a higher Mayo htTKV imaging class (1C–E), again confirming a lack of enrichment for patients with more rapid disease progression based on the trial design.

Encouragingly, no safety signals of concern (lactic acidosis or clinical hypoglycaemia) or treatment-emergent serious adverse events were detected in this study; lactic acid and vitamin B12 levels were also normal. Despite the Gastrointestinal Symptom Rating Scale (GSRS) being similar between both groups, by the end of the study, 22% of the patients in the metformin group had discontinued medication and 43% of the patients were intolerant of the maximal dose leading to dose reductions; only 35% were still on the prescribed dose of 2000 mg/d. Exploratory secondary endpoints showed a trend toward a positive effect of metformin on an annualized eGFR slope of 1.37 ml/min per 1.73 m² (P = 0.2) but an increase in mean annual htTKV of 1.68% (P = 0.38) and an increase in mean annual height-adjusted total liver volume (htTLV) of 0.39% (P = 0.72).

Thus, the TAME PKD study achieved its main primary endpoint showing that metformin at clinically relevant doses for type 2 diabetes mellitus (2000 mg/d) is safe in patients in the early stages of ADPKD (eGFR > 60 ml/min per 1.73 m²). Results of the exploratory secondary endpoints were, however, inconclusive, with nonsignificant trends for eGFR slope, htTKV, and htTLV. Since only a subgroup (35%) of metformin-treated patients were able to tolerate the
maximal dose prescribed (2000 mg/d), it is possible that a positive effect on kidney or liver volumes could have been missed due to suboptimal dosing. A second possibility could be that the patient cohort recruited had disease too mild to show a detectable effect on disease progression within the study duration. The results on safety and tolerability reported here should, nonetheless, apply equally to patients with more rapidly progressive disease, as would be the anticipated trial population in a future phase 3 renoprotection study.

The authors estimate that ~700–800 patients with ADPKD will be needed for a 4-year phase 3 RCT to detect a 25% improvement in an annualized eGFR slope or a 45% annualized htTKV slope with 80% power, assuming an overall 15% attrition rate. Based on the results of TAME PKD, this could be difficult to achieve without major adjustments in trial design to improve tolerability of the maximal dose (e.g., the use of a slow-release metformin preparation) and enrichment strategies (Mayo imaging class) to select patients with more rapidly progressive disease. What should be an optimal dose for ADPKD remains open. The inclusion of surrogate biomarkers of renal AMPK and mTOR activity (e.g., urine metabolomics, exosomes) and the measurement of plasma metformin concentrations in a future trial could help align any observed therapeutic benefits with its proposed mechanisms. Finally, clarifying a potential effect of metformin on total liver volume in an adequately powered future trial would be an important outcome distinguishing it from tolvaptan.

The potential for metformin to slow both kidney and liver disease in the early stages of ADPKD remains tantalizingly open. The TAME PKD study takes us one step closer, but further steps will need to be taken. In this respect, it is of interest that the Implementation of Metformin Therapy to Ease Decline of Kidney Function in Polycystic Kidney Disease (IMPEDE-PKD) trial is expected to begin enrolling later in 2021. This international multicenter study of 1164 patients with ADPKD selected for rapidly progressive disease aims to test whether metformin given as a slow-release formulation of 2000 mg/d over 2 years will improve the annual loss in eGFR compared to placebo (NCT04939935). This well-powered phase 3 trial should be completed in 2026, when we should have a definitive answer as to whether metformin has a role in the future management of ADPKD.

**DISCLOSURE**
ACMO reports having received grants and/or consultancy fees from Otsuka, ONO, Sanofi-Genzyme, Galapagos, and Mironid, companies working in the field of autosomal dominant polycystic kidney disease (ADPKD). All money is paid to his employing institution. RTG reports having received grants and/or consultancy fees from Galapagos, Ipsen, Mironid, Otsuka, and Sanofi-Genzyme, companies working in the field of ADPKD. All money is paid to his employing institution.

**REFERENCES**