to depression [5]. We recommend caution with interpreting data related to the association of depression, as assessed by the BDI, and mortality, especially in the elderly.

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**Editorial Note:** Dr Chilcot et al. had no further comments on this letter.

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**Clinical treatment of polycystic kidney disease (APKD): do we need further suggestions from rodents?**

Sir,

The article by Renken et al. [1] recently published in this Journal describes the effects of sirolimus (SRL) in the PCK rat, a model resembling human adult polycystic kidney disease (APKD) in which mTOR inhibitors had never been tested. In this study, oral treatment with SRL (2 mg/kg up to 12 weeks) did not attenuate cyst growth nor the progression of interstitial fibrosis compared to untreated control PCK rats and resulted in an impressive rise in bilirubin concentration [1]. These ‘negative’ data are in line with those recently reported by two large clinical trials on APKD, in which treatment with mammalian target of rapamycin mTOR inhibitors did not substantially affect cyst enlargement nor renal function [2,3].

In preliminary studies on the same rat strain, we have tested two different SRL doses: 0.2 mg/kg/day or 0.15 mg/kg administered 5 days a week (2 days yes/1 day off), both by intraperitoneal route. The higher dosage of the drug (n = 6), commonly used in Han-SPRD rats [4], determined a significant reduction in cyst volume [−34% versus untreated PCK rats (n = 6), P < 0.001] but caused marked hyperbilirubinaemia, a drastic reduction in body weight gain and a significant decrease in renal function compared to control rats. Low-dose SRL-treated rats (n = 6) showed a better body weight gain with respect to the higher dosage (15.4 ± 4 g/week versus 7.57 ± 2.3 of high dose, P < 0.02) and, interestingly, the cystic area remained significantly lower (~32% versus control, P < 0.03), with a significant decrease of total number of cysts and their maximal diameter. This lower dosage and the peculiar administration schedule also preserved both liver and kidney function. Unlike Renken’s study, we also found a significantly depressed activation of phosphorylated mTOR and of S6K protein in treated rats (western blot analysis).

The different outcomes of the two studies certainly reflect varying experimental conditions, like SRL dosage and its administration route, that resulted in different trough levels (1.63 ± 0.25 ng/mL in our study and 0.61 ± 0.06 ng/mL in Renken’s study): this could also explain the lower inhibitory effect on mTOR and S6K protein observed by immunohistochemistry in the latter study. Why Renken’s rat showed hepatic toxicity remains less clear since this side effect was not observed in our animals despite higher trough levels of SRL (different administration schedule, intrinsic hepatic susceptibility?).

Therefore, the same drug may elicit different results on the basis of its dosage, its bioavailability, the length of its administration or the presence of specific genetic patterns; accordingly, the study by Renken et al. should not be considered negative rather ‘not positive’. This could be true in clinical studies, too.

Walz et al. observed a reduction in cyst growth in patients treated with everolimus (24 months), not associated with an improvement in glomerular filtration rate (GFR), but their patients started with a reduced GFR, (averaging 53 mL/min); patients of Serra’s study with a well-preserved renal function (mean GFR: 92 mL/min), conversely, showed no change in cyst volume nor in GFR after SRL treatment, but these latter patients were administered low doses of SRL (averaging 1.5 mg/day per os), only for 18 months. These peculiar methodological aspects might have precluded more favourable results.

Indeed, despite animal studies suggest that treatment with mTOR inhibitors should start very early (i.e. when renal fibrosis and compensatory renal hypertrophy are still absent) and that adequate doses of such drugs must be used, this policy seems unfeasible in clinical practice either for the cost of treatment and the unavoidable occurrence of side effects. Probably, we need further experimental preclinical studies addressed to find out specific associations of SRL with different drugs that may be administered in sequence and with long drug-free periods [5]: we are currently testing new anti-apoptotic agents and cyclic adenosine monophosphate inhibitors. We believe that this is the only way to partially overcome the obvious difficulties of clinical treatment that should be started early but must be safe and affordable in the long term.
Conflict of interest statement. None declared.

Editorial Note: Dr Renken et al. had been invited to reply to this letter but we did not receive a response.

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