Reviewer’s report

Title: TNF-alpha blockade is ineffective in animal models of established polycystic kidney disease

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Reviewer: Gopi K Rangan

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In this study, the authors have investigated the effects of etanercept on the progression of cystic renal disease in two genetically orthologous small animal models of PKD (pck rat and Pkd2 ws25). The findings of the manuscript:

(i) Eternacept (0.5, 5 and 10 mg/kg i.p.i q3d) reduces the phosphorylation of NF-kB, ERK and p38 in kidney lysates of PCK rats (by at least 50%) following 4 weeks of treatment;

(ii) Treatment of PCK rats with 5mg/kg of eternacept from day 28 until day 96 did not alter KW:BW, cyst number or serum creatinine

(iii) Treatment of pkd2 model of ADPKD (either from week 13 to 21 or from week 4 to 12) similarly did not alter KW:BW ratio, cyst number or BUN.

The authors conclude that etanercept does not affect disease progression in these models and therefore may not be useful in the clinical management of patients with ADPKD.

Major comments

This is a well written manuscript that makes an important point regarding the feasibility of using TNF-a blockade in the long-term therapy of PKD. However, unfortunately, the manuscript lacks detail in both the Methods and Results, making it difficult to be certain of the Conclusions.

1. The methodology used to assess the severity of cystic renal disease has been completely omitted. Cyst number per field alone is insufficient to assess disease severity, and usually accompanied by other methods, typically, percentage cyst area. On page 7, the authors state that “cyst number and cyst area were not reduced”. However, no data on cyst area is provided in Table 2. The authors should also consider providing photomicrographs of kidney histology from the key treatment groups.

2. Data on interstitial inflammation (e.g. CD68/ED-1) and interstitial fibrosis (e.g. picrosirius red staining) should be provided given that eternacept might suppress both of these parameters.

3. Page 8: the authors state that “vasopressin and mTOR antagonists have largely been ineffective”. This statement is surprising as the TEMPO ¾ trial revealed positive effects on kidney enlargement, kidney function and
ADPKD-related symptoms, and the authors acknowledge this fact in the first paragraph of Page 7.

4. The authors also test the efficacy of 0.1% mozavaptan in the two animal models. This is an important set of experiments, but the rationale for including them in the present manuscript is not clear, and confuses the conclusions.

5. Please provide more information on which phosphorylated “NF-kB” protein is suppressed by etanercept (Figure 1). Is it p65?

Minor comments

Page 1: The abstract is well written, but lacks detail of the Methodology and Results contained in the manuscript. For example, the Methods section is an “Aim” rather a description of the Methods used. The term “inflammatory markers” in the Results is not specific. The type of animal model used is not mentioned etc.

Page 4: How were the Pkd2 mice genotyped?

Page 5: “rates” should be “rats”

Page 5: Forced manual voiding in rats is an unusual method of urine collection. Why wasn’t urine collected in metabolic cages, like for the mice?

Page 6: How old were the Pck rats at the start of eternacept dosing experiments?

Page 6: Mid-page: Define “PDK”

Page 10, Table 2: Data on urine production is not provided for all groups?

Figure 2: Figure Legend is not provided

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.