University of Groningen

Doubts about the efficacy of tolvaptan for polycystic kidney disease Reply

Gansevoort, Ron T.

Published in:
CLINICAL NEPHROLOGY

DOI:
[10.5414/CN109927Reply](https://doi.org/10.5414/CN109927Reply)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gansevoort, R. T. (2020). Doubts about the efficacy of tolvaptan for polycystic kidney disease Reply. *CLINICAL NEPHROLOGY*, 93(6), 310-311. <https://doi.org/10.5414/CN109927Reply>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

©2020 Dustri-Verlag Dr. K. Feistle
ISSN 0301-0430

DOI 10.5414/CN109927Reply
e-pub: January 30, 2020

Reply to Dr. Anderson's letter

Ron T. Gansevoort

*University Medical Center Groningen,
Groningen, The Netherlands*

Sir, – Thank you for inviting me to write a reply to Dr. Anderson's letter. Let me start by making clear that I have a conflict of interest. I have been a member of the Steering Committee of several trials with tolvaptan [1, 2] and have treated many ADPKD patients with this drug. Notwithstanding, I would like to respond to Dr. Anderson's comments.

Some of the initial trials with tolvaptan in ADPKD were indeed overpowered. This does not question the statistical significance, as suggested, but could question what the clinical relevance is of these statistically significant findings. Personally, however, I do not question their clinical relevance (see below).

It is stated that the TEMPO trial was managed by nephrologists with expertise in ADPKD at a major USA medical center. Please note that actually many centers around the globe were involved, with many nephrologists without specific expertise in ADPKD. This lends the findings appropriate external validity.

Dr. Anderson states that he is skeptical about the clinical relevance of the drug effect on renal function and refers to sCr findings. Nowadays, as also discussed in a recent KDIGO meeting, slope of eGFR is accepted by the nephrological community, the FDA, and the EMA as a valuable clinical endpoint [3, 4]. Slope of eGFR loss is 30 – 37% less with tolvaptan [1, 2]. This translates roughly as for every 3 years of tolvaptan treatment, a 1-year later start of kidney replacement therapy. For a disease where there is no alternative treatment, and where life-long treatment with tolvaptan is a possibility, this is in my opinion a clinically relevant benefit.

The drug indeed blocked the deterioration of eGFR by 1.27 mL/min per year. As stated above, we regard that as a 30 – 37% reduction in rate of eGFR decline. However, given that the rate of eGFR decline in

the placebo groups was –3.70 mL/min per year, and that age-related decline in eGFR is ~ 1.00 mL/min per year, one could theoretically also argue that ADPKD causes an additional 2.70 mL/min per year decrease in eGFR on top of what is seen normally with aging. This is decreased by 1.27 mL/min per year by tolvaptan. This is actually a reduction in rate of disease progression by 43% (1.27 divided by 2.70). This does not seem to be a miniscule change.

I fully agree that the effect on total kidney volume (TKV) is limited. Most of the effect is indeed seen in the first months of treatment, with relatively limited effect thereafter. In my opinion, this questions whether the effect on TKV drives the renoprotective effect, and suggests that additional non-TKV-related mechanisms may be in play.

An effect on appetite and on meat intake may theoretically cause some decrease in serum creatinine (and increase in eGFR) in the short term but is unlikely to cause a growing difference in serum creatinine (and eGFR) over 3 years of the study. Moreover, there was no acute decrease in creatinine. In fact, there was even an acute increase in creatinine, which argues against this hypothesis.

You question the relevance of extrapolating trial efficacy data to a long-term horizon. Of course I respect such a view. However, it should also be noted that such an analysis is requested by regulatory authorities (FDA, EMA, Canadian, Australian, etc.), and that in general the pharmacoeconomic experts of these authorities all agreed with these extrapolated data.

Funding

Not applicable

Conflict of interest

Dr. Gansevoort has been a member of the Steering Committee of several trials that studied the effect of tolvaptan in ADPKD (TEMPO 3:4, TEMPO 4:4, REPRISE) and received several grants from Otsuka for investigator-driven research. All money is paid to the employing institution.

References

- [1] *Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; TEMPO 3:4 Trial Investigators.* Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med.* 2012; 367: 2407-2418. [CrossRef](#) [PubMed](#)
- [2] *Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, Ouyang J, McQuade RD, Blais JD, Czerwiec FS, Sergeyeva O; RE-PRISE Trial Investigators.* Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med.* 2017; 377: 1930-1942. [CrossRef](#) [PubMed](#)
- [3] *Grams ME, Sang Y, Ballew SH, Matsushita K, Astor BC, Carrero JJ, Chang AR, Inker LA, Kenealy T, Kovesdy CP, Lee BJ, Levin A, Naimark D, Pena MJ, Schold JD, Shalev V, Wetzels JFM, Woodward M, Gansevoort RT, Levey AS, Coresh J.* Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: An individual participant meta-analysis of observational data. *J Am Soc Nephrol.* 2019; 30: 1746-1755. [PubMed](#)
- [4] *Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, Simon AL, Ying J, Beck GJ, Wanner C, Floege J, Li PK, Perkovic V, Vonesh EF, Greene T.* GFR slope as a surrogate end point for kidney disease progression in clinical trials: A meta-analysis of treatment effects of randomized controlled trials. *J Am Soc Nephrol.* 2019; 30: 1735-1745. [PubMed](#)

Correspondence to
Dr. Ron T. Gansevoort
Professor of Medicine
University Medical Center Groningen
Groningen
The Netherlands
r.t.gansevoort@umcg.nl