Author's response to reviews

Title: Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol of a randomized clinical trial

Authors:

Melissa Chrispijn (M.Chrispijn@mdl.umcn.nl)
Joost PH Drenth (joostphdrenth@cs.com)

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Author's response to reviews: see over
Dear Editor-in-Chief,

Please find enclosed the revised version of our manuscript ‘Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol of a randomized clinical trial’ (Manuscript number 2041726421576608), which we would like to contribute to Trials.

We thank you for considering our manuscript for review and we thank the reviewer for his constructive comments and we are pleased to answer. We have completed a point-to-point reply which can be found below. We have marked the changed or added parts in the manuscript using a red and underlined font and we have indicated the page and line number for ease of reference.

We sincerely hope that this version is fit for publication in the Journal.

Joost PH Drenth, MD, Ph.D.

Professor of Molecular Gastroenterology & Hepatology
Department of Gastroenterology & Hepatology
Radboud University Nijmegen Medical Centre
P.O. Box 9101, code 455
6500HB Nijmegen
The Netherlands
Cell +31 629501892
Tel +31 24 3614760
Fax +31 24 3540103
E-mail joostphdrenth@cs.com
Point-to-point reply

1. The authors indicate that there are two major genetic distinct disorders – PCLD and ADPKD - is it possible that there will be a differential response to the combination over the monotherapy according to underlying genetic cause?

Indeed PCLD and ADPKD are two major genetic distinct disorders who share the phenotype of polycystic liver. The LOCKCYST trial performed by van Keimpema et al. showed no statistically significant difference in effect of lanreotide between the PCLD and ADPKD patients. Our trial was not designed to address this issue. Through a separate line of research we plan to perform an individualized meta-analysis including all patients who have received octreotide or lanreotide in a RCT order to investigate the effect of different patient factors on therapy.

2. The authors mention surgery as the invasive alternative with no convincing evidence of benefit - will those randomised all not have had this surgical option? And what about post randomisation? Will surgery be banned? Likewise, what about other mTOR drugs and/or additional somatostatin analogues as rescue interventions? Will these be allowed?

Our trial contained the stipulation that patients who have had surgery within three weeks before start of the trial were excluded from the trial. The same holds for the use of mTOR inhibitors and (other) somatostatin analogues. Patients are not able to commence the trial if they have used one of these drugs in the three months preceding randomisation. In Table 2 we have shown the exclusion criteria of the trial. In addition, other mTOR inhibitors and somatostatin analogues are not allowed as rescue interventions during the trial. Likewise surgical interventions for polycystic liver disease during the trial are disallowed, as is stated in the paragraph “Withdrawal of individual subjects” on page 7.

3. The trial is open - the authors should discuss more fully why it was not feasible to create a dummy for the everolimus? They just say in the discussion that the monitoring of everolimus effectively unblinds the trial - more detail is needed. And also why the specific choice of everolimus at that dose and frequency?

We have decided not to use a dummy, because we will monitor everolimus trough levels and thereby effectively unblind the therapy. In addition, we expect that patients will have significantly more side-effects resulting from everolimus treatment than from octreotide. Patient will recognise this and therefore blinding will be ineffective.

We elected to use a therapeutical range of everolimus in correspondence with that in transplantation medicine (3-8 ng/mL). The prescribed dosage and therapeutical range are accepted within the community of transplant physicians. This has led to a wealth of data that support the use of this specific dosage in transplanted ADPKD patients. We have extended the discussion on this topic (p. 12, l. 24-p.13, l.1-2).

4. The study is single centre - the authors should discuss here in the protocol what limitations that is likely to place on the generaliability of whatever the findings are? Likewise the list of inclusion and exclusion criteria in table 2 looks extensive - so roughly what proportion of those that might be considered for this treatment if successful are excluded from this evaluation?

The fact that this study is single centre may be a limitation. Fact is that our centre is the only tertiary referral centre in The Netherlands for the pharmacological treatment of polycystic liver disease. Patients come from a geographically wide area well beyond the catchment region of our centre. Therefore the targeted population reflects the symptomatic PLD population in The Netherlands which is a token of generalisability.
The prevalence of PCLD (>20 liver cysts) is estimated to be 1/158,000², which comes down to a PCLD population in The Netherlands of ~100 patients. The majority of these patients was excluded based on the inclusion criteria age (18-70 years), liver volume (>2500 mL) or severity of the disease (at least 3 PLD symptoms, as stated in Table 1). That leaves about 50% of the population for screening. Only three patients were excluded based on our extensive list of exclusion criteria.

5. Primary outcome - will the change in total liver volume at 12 months be assessed by a technician/CT operator unaware of what treatment was randomly assigned? The authors say 'CT scans will be anonymized to allow blinded assessment of the liver volume' - so this is reassuring - but more explicit detail is needed on this important methodological issue.

The primary outcome will be assessed by a clinical researcher (MC) who is the first author of this manuscript. All CT scans will be anonymized and all dates will be removed, so the clinical investigator is unfamiliar which CT scan belongs to which patient and whether the CT scan is dated prior to treatment or after treatment. We have added this to the paragraph “Randomization, blinding and treatment allocation” (p. 5, l. 20-22).

6. And likewise the authors give useful data on intra and inter observer variability, but do not seem to say who will be taking the 12 month scan and whether this will be the same operator that took the baseline scan?

We have previously analysed the interobserver and intraobserver variability of target volume delineation. Using multiple independent assessors we obtained correlation that exceeded r=0.95 for CT liver volume measurement¹. In the proposed trial both CT scans (prior and after drug treatment) will be assessed by the same operator. The CT scans from the ELATE trial will be reassessed blindly by an independent investigator (TG). Given our previous experience we think that the interobserver variability will be limited. For clarity reasons, the same operator will assess the scans that have been taken prior and after the trial in one run in order to limit the intraobserver variability. We have added to the paragraph “Randomization, blinding and treatment allocation” that all CT scans will be measured by these two researchers (p. 5, l. 22-23).

7. The authors are looking for a huge effect size: a difference of 166 ml with an assumed standard deviation of 130 (or an ES of ~1.3). The obvious concern is that a smaller but nonetheless worthwhile improvement e.g. a doubling with an extra 60 mls, will be missed. Also, is this the standard deviation of the change over baseline? That should be smaller than either the baseline or the 12 month SD.

We indeed seek a large effect size. Qian et al. retrospectively measured the volumes of polycystic livers and kidneys in patients who had ADPKD and received kidney transplants and participated in a trial that compared a sirolimus-containing immunosuppression regimen with a tacrolimus-containing regimen. Sixteen patients received computed tomography or magnetic resonance imaging scans. Treatment with the sirolimus regimen for an average of 19 months was associated with an 11.9% reduction in polycystic liver volume, whereas treatment with tacrolimus for a comparable duration was associated with a 14.1% increase. The difference between the sirolimus regimen and non-sirolimus regimen is larger than 20%³. Therefore we thought that an effect size of 166 ml (3.7% based on a mean liver volume of 4500 mL) is a realistic target. We have expanded on this issue on page 12. The standard deviation of 130 ml is based on the findings in the LOCKCYST trial¹. We assume that the standard deviation of the change in liver volume between baseline and 12 months between the two groups will be in the same range, as changes in liver volume often have a large range. We also observed that the SD of the change is indeed lower than that of baseline or 12 months.
8. What percentage of the baseline liver volume does a reduction of 166 ml represent? Is it possible that those with smaller livers will struggle to achieve that absolute level of change? Did the authors consider a percentage change, or is it an absolute change above a threshold that will deliver the anticipated benefit?

At this moment we do not know what the baseline liver volume is, but the liver volume has to be at least 2500 mL to participate in the trial. If we assume that we have in our sample a mean baseline liver volume of 2500 mL, 166 mL would be a relative reduction of 6.6%. We expect that the mean liver volume in the total group will be around 4500 mL (in line with the LOCKCYST trial), so that is a relative reduction of 3.7%. It is indeed possible that patients with smaller livers will not to achieve this effect size, that is why we elected to include patients with a large polycystic liver (>2500 mL). We do not know whether a threshold must be reached to have a beneficial effect on liver volume and symptoms.

9. How are the authors going with deaths and loss to follow up - they have added a couple of subjects assuming a 10% loss, but under intention to treat they should have a plan to deal with these missing data?

We have indeed included an additional 10% more patients to account for drop-outs. This will allow us to reach our calculated sample size and thereby have a robust chance to find the proposed difference in liver volume. However, if patients will get lost to follow-up due to death, severe side-effects or otherwise, we will include them in an Intention-to-treat (ITT) analysis as this is the recommended method in superiority trials to avoid any bias. When patients have prematurely terminated the trial, they are asked to undergo a CT scan after stop of treatment. These values will be used instead of end-of-treatment values for ITT-analysis. When no CT scan is available after premature termination of the trial or the patients drops out in the first month of the trial, the value at start of treatment will be used for ITT-analysis. We use “last value carried forward” for missing observations other than CT scan. We also perform parallel Per Protocol analyses next to the ITT-analyses. We have described this in more detail in the “Statistical analysis” section on page 9, line 7-12.

10. The definition of Per Protocol looks pretty strict - with only about 20 per group maximum, will this be a viable analysis?

We will perform the results by a per protocol analysis as well as a intention-to-treat analysis. If done alone, per protocol analysis leads to bias. This definition of Per Protocol analysis is indeed strict, but we wanted to know that the therapy has been given following the predefined treatment protocol and that the effect is not influenced by treatment protocol violations. Furthermore we have a reliable patient population, so we think this will be indeed a viable analysis.
Reference List

