Author's response to reviews

Title: Treatment with Tolvaptan: a rapid and efficient hyponatremia management in patients with SIADH and small cell lung cancer

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Author's response to reviews:

Response to reviewer: Donal O'Donoghue
Reviewer's report
Title: Tolvaptan treatment leads to a rapid and efficient hyponatraemia management in patients with SIADH and small lung cancer (SCLC)
Version: 3 Date: 29 June 2012
Reviewer: Donal O'Donoghue
Reviewer's report:
This is a small uncontrolled study in a single centre that describes 10 cases of SCLC HN accumulated over an 18 month period managed by a trial algorithm that defines mild moderate and severe HN differently depending on whether persistent or acute/recurrent and presents no aggregated data to support the claims of clinical utility of tolvaptan in this situation. Safety is also claimed despite the admission that rapid correction of Na occurred in some cases. Benefit is claimed no measures are given.

We thank the reviewer for his helpful suggestions and would like to answer:

There are only insufficient prospective data sets about the treatment of very severe cases of SIADH caused by small cell lung cancer (SCLC) in the current literature. The description of ten cases which were treated and followed according to the algorithm as shown is by far the largest series by now. In particular, no data exist in cases of
hyponatremia below 125 mmol which were treated with an oral vasopressin antagonist such as tolvaptan in SCLC patients. Therefore, the study is the first to show and provide data about the effectiveness of this treatment option in very sick patients which require emergency treatment in a palliative situation. The data set shows that improvement of sodium levels correlated with improvement of quality of life scores (see graphs). Quality of life scores are accepted as the standard measure in palliative care settings like this one (see Temel et al NWEJM 2010). The patients were treated according to the manufacturers suggestions and one, important key finding of the study is that the minimal suggested dose (15 mg) might lead to “overshooting” of sodium levels in some patients, a very important finding of pharmocovigilance and was reported as such. This is the first description of a finding such as overshooting without clinical impediment and important to review and report to the community of thoracic oncology, who treats patients with SIADH. The benefit of the treatment of a patient in a palliative care setting is measured by both quality of life and corresponding time frame which is left for this patient. We were able to show that with rapid treatment of hyponatremia the patients quality of life improved and the patient life span was improved.

The cases are hypothesis generating rather than proof of principle that tolvaptan improves the management and QoL in SCLC with HN.

The hypothesis was that rapid intervention of hyponatremia leads to QoL improvement and rapid discharge of the hospitalised patient with improved of his cognitive function to enable this. This hypothesis was verified in this study, furthermore we gathered important data about the pharmocovigilance and the time frame how to treat and when to treat. This is the first series to do so
in this field.

Background discussion is somewhat superficial for the intended audience and add little to our understanding. Dissappointing the literature on difficulties with chemotherapy and link between HN and prognosis is not reviewed in any depth. what is the basis for the claim re length of stay and admissions - none is presented. What is an excellent clinical response - no definition eg in terms of ECOG is given.

This is the first extensive series of patients who were treated with this therapeutic option in a potential lethal condition of very severe SIADH. Both the success of correction of SIADH and the survival benefit after the treatment are new to the community. Therefore, both the literature in this field and the comments on potential other therapeutic options remains restricted. The format of the submitted manuscript was pointing at the improvement of QoL and survival after intervention. Both criteria were met successfully.

Due to the fact that tolvaptan is prescribed and administered in an out- and inpatient setting which varies considerably in the countries where it has been approved we focused on our extensive experience how effective treatment improves the QoL and survival of these patients.

Recommend rewrite as a case series of experience and address the above with in the discussion.

We did

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Quality of written English: Needs some language corrections before being published
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'
Reviewer's report
Title: Tolvaptan treatment leads to a rapid and efficient hyponatraemia management in patients with SIADH and small lung cancer (SCLC)
Reviewers Report:
This manuscript provides an interesting analysis of the use of the vasopressin-2 receptor antagonist, tolvaptan. The authors describe their study as a proof of principle study of 10 patients treated at their institution who received tolvaptan. However in the abstract they state that they ‘prospectively analysed if efficient HN management with tolvaptan in patients with SCLC and SIADH leads to an improved disease management and increase in quality of life’. They go onto conclude that ‘tolvaptan leads to a rapid and efficient amelioration of the ECOG-Index and control of the underlying disease’. By ‘disease’ it is unclear if the authors are referring to SCLC or HN and this needs to clarified and it may be better to replace the word ‘disease’ with pNa or HN.

This article will require revision before being accepted.

Major Compulsory Revisions:
1. Within the abstract, the authors state that ‘tolvaptan leads to a rapid and efficient amelioration of the ECOG-Index and control of the underlying disease’. However data has not been presented with this manuscript to support this claim. The graphs appear to demonstrate an improvement in ECOG status in less then 50% of patients which could be attributed to the use of tolvaptan. These patients also received standard chemotherapy which may account for disease (cancer or pNa) control and the overall survival of these patients is within the range that would be expected for this group who all received systemic chemotherapy.

We added new data to the set of clinical observations and reviewed the clinical data reports.

The patients received chemotherapy after the sodium levels were stabilized. Therefore we claim that initial stabilization lead to an uneventful followup of the patients and the omission of emergency hospitalisation due to effective hyponatemia management.
We followed a series of patients and could show that a reproducible pattern was shown. Effective hyponatremia management lead to stabilization of the clinical course and in turn was followed by the administration of an effective tumor treatment.

2. The presentation of further data would add to this manuscript, maybe in tables. For example changes in ECOG from before and after tolvaptan, alterations in pNa, time to normalisation of pNa, median number of days of tolvaptan treatment needed plus a range, duration of maintenance of pNa and number of patients who required repeat courses. Whilst this data is available in the supplementary data, it is difficult to tease out these parameters. We modified the graph and tables to clarify these points within the limitations of a case series report.

3. No data are provided to demonstrate alterations in morbidity (?neuro-psychiatric) despite this data being collected in the methods section and ‘significant clinical’ improvements referred to in the discussion and results but the nature of these improvements is unclear. In this case series we focused in this case series on the ECOG status which encompasses the overall health status to facilitate the comparability of the graphs.

4. The conclusions do not take into account that many patients received systemic chemotherapy at the same time or after starting tolvaptan. This needs to be acknowledged.

As shown above before we started chemotherapy after hyponatremia management was effective To optimize the effects of the chemotherapy.

Minor Essential Revisions:
1. Table 1 uses the German term ‘Nierenfunktion’ and ‘NNR’/
2. Table 1 uses ‘Na< 12+5’
3. Table 1 some of the track changes are visible
4. Table 2 the terms ‘cerv’, ‘pulm’, ‘oss’ and ‘hepar’ have not been explained in the legend.
5. The abbreviation of small cell lung cancer is (SCLC) in the first paragraph of the background section, but then this is not used in later paragraphs. The abbreviation is then reintroduced as if new in the results and discussion section.
6. The abbreviation ‘SCLC’ is not described in the abstract.
7. The English needs reviewing e.g. two full stops next to each other and spaces before full stops.

Discretionary Revisions:
1. In the methods section, the discussion in the second paragraph about cardiovascular drugs would be better explained in the background section.
2. It might be useful to refer to table 1 in the method section, maybe where the treatment algorithm is referred to.

We changed the errors in the text as mentioned and would like to thank for the helpful comments.

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

Quality of written English: Needs some language corrections before being published.

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.