Author's response to reviews

Title: Bladder sensory desensitization decreases urinary urgency

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Response to reviewers
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MS: 6406335138169067 - Bladder sensory desensitization decreases urinary urgency
Carlos Silva, Joao Silva, Helder Castro, Frederico Reis, Paulo Dinis, Antonio Avelino and Francisco Cruz

Dear Biomed Central Editorial Team

Regarding our recently submitted manuscript "Bladder sensory desensitization decreases urinary urgency" we are sending a revised version of the manuscript which I hope will address the reviewers’ comments. We thank the reviewers for their critique of our work. Their suggestions helped us to improve our paper. The revisions included in the manuscript and responses to issues raised by the reviewers are as follows:

Reviewer Clare Fower
Major Compulsory Revisions

Issue 1)
"As a preliminary report, this is important. With the increasing expense and regulation of clinical research, well conducted pilot studies are extremely valuable. Without them neither "own investigator" nor commercially sponsored studies, will be initiated, with serious consequences for future pharmacological discovery. The authors should perhaps give the dates as to when this work was done since presumably it was before the recent European Regulations were enacted in Portugal"

Reply:
This work was done during 2005, before the European regulations were enacted in Portugal. This data is now in the text (Methods, page 5, line 11).

Issue 2)
"This particular group of workers have had greater success than many others in obtaining therapeutic benefit from very low concentrations of RTX and the findings here provide additional supportive data for the efficacy of a 50 nM dose. Perhaps the fact that they have had these results using such a low dilution should be stressed"

Reply:
We agree the suggestion and this is now stressed in the end of the manuscript (page 13, lines 1-3).

Discretionary Revisions
"The paper states "this study was presented in part elsewhere [20]." Some further information about this should be given. Reference 20 is an abstract. Does this simply mean the findings have been presented at a scientific meeting?"

Reply:
The findings have been presented at the 2006 European Congress of Urology and published in the abstract book. This is now clarified in the text (page 5, line 8).
Reviewer Apostolos Apostolidis

Major Compulsory Revisions

Issue 1)
"Were the patients submitted to UDS and did they all have DO or increased bladder sensation? This is an important point, as urgency perceived by patients with DO is probably of different pathophysiology to urgency experienced by patients with non-DO OAB (increased bladder sensation). Please clarify".

Reply:
In the present study the patients did not had urodynamics at patients's selection or during the study. The only criterion was the presence of urgency. This is stated at Methods (page 6, lines 15-17). However, we agree with the suggestion which is now stressed in the conclusions (page 13, lines 4-7).

Issue 2)
"Was bladder outlet obstruction an exclusion criterion? Please clarify"

Reply:
Patients with symptoms suggestive of bladder outlet obstruction were excluded (Methods, page 5, lines 17-18).

Issue 3)
"Why was a decrease in urgency episodes of 25% or more considered as cut-off for good clinical response? Is there previous experience/literature to document this? This is significant as OAB studies of the last 5 years show a placebo response at the level of 4-50%.

Reply:
Some studies are applying a minimal cut-off to give to the reader the magnitude of the change in absolute terms (for example Chapple et al used the cut-off 30, 60 and 90%; see Chapple et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJ U Int 2005; 95: 993-1001). We decide to follow the same idea. The placebo effect found in the present work is in agreement with the majority of OAB studies.

Discretionary Revisions

Issue 1)
"Animal experiments in TRPV1 knockout mice have shown that TRPV1 is necessary for the adequate release of ATP from the urothelium. Could that be a more possible mechanism for reduction of urgency via a decreased activation of suburothelial P2X3 which has been shown to correlate with level of urgency than a possible decrease in NGF?"

Reply:
We agree with re reviewer. We made the appropriate changes (page 11, lines 17-22 and page 12, lines1-2) and included a new reference (Birder et al. Nat Neuroscience 2002; 5: 856-860)

Issue 2)
"Another question is whether there is evidence to support that a reduction in TRPV1 leads to a decrease in the release of NGF from the urothelium? NGF is regulating the expression of TRPV1, but is that happening vice versa as well as the authors are proposing in the hypothesis?"

Reply:
This is only an hypothesis. We rephrased the text in page 11, lines 13-16.

Issue 3)
"We would be careful in accepting the presence of TRPV1 in interstitial cells - the paper by Ost et al used an antibody against the vanilloid receptor like 1, which is equivalent to TRPV2."

Reply:
We agree with the reviewer and we add the word "possibly" (page 4, line 3)
Issue 1)
"page 5, Methods. What are the inclusion criteria of OAB to enter this study?"
Reply:
Patients had to have refractory OAB as stated in page 5 and line 11 (Methods).

Issue 2)
"Methods. Among 23 patients with refractory OAB enrolled in this study, how many patients had neurogenic origin and how many patients were classified as idiopathic?"
Reply:
Done in page 5, lines 11-12

Issue 3)
"Were there any differences in the effect of RTX on OAB symptoms (urgency, urgency incontinence and frequency) between idiopathic and neurogenic OAB groups?"
Reply:
The small number of neurogenic OAB patients prevented such analysis.

Issue 4)
"Fig. 2. Are the differences between vehicle and RTX in percentage of patients with a 25% or more decrease of urgency episodes and in percentage of patients with subjective improvement statistically significant?"
Reply:
Statistics are now in the text (Methods, page 8, lines 4-6; Results, page 8, lines 17-20) and in the figure 2

Issue 5)
"Kuo HC reported that a significant increase in postvoid residual after multiple intravesical instillation of RTX (10nM) in patients with detrusor overactivity refractory to anticholinergics (BJU Int, 2005; 95(7): 1023-7). How about the changes in voiding efficacy and postvoid residual after RTX treatment in the present study?"
Reply:
We did not perform urodynamics or measure the post void residual in any of our patients. None of the patients complain of difficulties in emptying the bladder. In our previous experience with RTX we never had cases of urinary retention. Nevertheless we state that "After RTX treatment none of the patients reported difficulties in emptying the bladder"(Results, page 9, lines 10-11).

Issue 6)
page 5, line 2, "effect of RTX in urgency " can be corrected to "effect of RTX on urgency".
Reply:
We have made the correction.

We hope that our revised manuscript is suitable for publication
Sincerely

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Portugal