Reviewer’s report

Title: Use of ivacaftor in late diagnosed Cystic Fibrosis monozygotic twins heterozygous for F508del and R117H-7T – a case report

Version: 1 Date: 25 Feb 2019

Reviewer: Fernando Marson

Reviewer’s report:

REVIEW

The authors performed an extensive and great correction through the manuscript. Now, we are able to conclude about the importance of the main findings. However, before to be publish some aspects should be revised.

(i) CFTR mutation should be written in Italic type. Also, I believe that the term "mutation" should be revised to "pathogenic variant";

(ii) the term polymorphism could be written as "variant or common variant";

(iii) F508 should be written as F508del;

(iv) the sweat test with values of 52 and 41 mmol/L is not pathogenic. In this case, I believe that the authors should state "borderline value";

(v) the authors could state the possibility of cis and trans condition. VERY rare case scenario.

(vi) Both sentences "Surprisingly, even in monogenetic twins, the clinical response and side effects of ivacaftor therapy varies widely. In addition to the existing CFTR base defect, there seems to be other factors that influence not just the phenotype and the disease severity but also the response and onset of side effects [37]." AND "Our case shows that response to CFTR modulator therapy is not predictable, even in monogenetic twins." are not correct. The own author and the reviewers suggested the presence of previous disease as a problem to evaluate the response in use of spirometry, as follow: "In addition, as in our case, an already occurring, irreversible structural lung damage can be regarded as a cause why response of lung function during therapy with ivacaftor, despite identical genetic information, is so different."

(vii) The follow statement and idea behind it should be revised: "Even a change in sweat chloride is controversial as a marker for response to a CFTR-modulating therapy, because sweat chloride changes in response to ivacaftor do not correlate to FEV1 changes.". Both, FEV1 and sweat chloride have limitations to be used as a marker of response. Also, there is no correlation because the FEV1 shows a reduction through the life and the sweat chloride shows a variability with a non-linear proportion. Also, the drugs in use to perform the precision medicine correct the CFTR expression and the CFTR expression can be analyzed in use of sweat chloride. However, we
need to improve the quality of the sweat chloride or to have a standardization to do the test or to include other types of tests to measure the CFTR function;

(viii) Figure 1 is incorrect. Please, the authors should revise the values (FEV1 ~80 in both cases).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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