**Reviewer’s report**

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

**Version:** 0 **Date:** 02 Oct 2018

**Reviewer:** Manu Jain

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In this case report the author's present monozygotic CF twins with the genotype F508del and R117H/7T who have different clinical courses and response to ivacaftor therapy. Specifically two CF patients, twins, were diagnosed with CF at the age of 55. Each was found to have two mutations in the CFTR gene (Delta F508 and R117H/7T), with pathological sweat chloride value, though not diagnostic. Despite being twins and living in the same environment the patients have a different severity of the disease with different lung involvement. Ivacaftor was initiated and both response and side effects were significantly different in each patient. In the less affected patient, there was an improvement in lung function and a normalization of the sweat chloride. In the severely affected patient, no increase in FEV1 was seen, but there was a reported decrease in exacerbation and hospitalization rate and weight gain. The less affected twin had an increase in FEV1 and an improvement in sinus symptoms.

**Critique**

Differences in the clinical course of CF patients with identical genotypes, even within the same family is well-known to occur and has been previously reported many time. Thus this finding is not particularly novel, especially in light of the fact that 1 twin was chronically infected with Pseudomonas aeruginosa and one was not. The authors’ state that the patients were monozygotic, which would potentially make this report more interesting, but do not provide evidence for this. Additionally though the author's try to make the claim that there was a differential response to ivacaftor, in fact both patients do demonstrate a clinically meaningful response to ivacaftor therapy. In addition the sweat chloride values are essentially the same after initiating ivacaftor. It is well know that sweat chloride changes in response to ivacaftor do not correlate to FEV1 changes and that ivacaftor treated patients demonstrate differential clinical responses. Thus the novelty of this report is limited. There are other issues listed below that limit enthusiasm.

* TID dosing for ivacaftor is not the usual dose

* How was a reduction in exacerbation rate quantified for the 1st patient.

**Are the methods appropriate and well described?**

If not, please specify what is required in your comments to the authors.

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

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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Acceptable

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