Reviewer's report

Title: In vitro prediction of stop-codon suppression by intravenous gentamycin in patients with cystic fibrosis; a pilot study.

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Reviewer: Godfried M. Roomans

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General

The authors have investigated the effect of gentamycin treatment on CF-patients with a stop mutation ("class I") both in vitro and in vivo. The in vitro results (gene readthrough levels) were used to predict the (sub)type of mutation that would be most sensitive to gentamycin treatment. This was confirmed by the in vivo experiments, showing a modest improvement for CF-patients with the Y122X mutation, but no improvement for patients with other mutations.

The study is well-planned, and the end-point measurements use well-established and acceptable techniques. I have no technical criticism of the paper.

The important and novel positive result of the paper is that gentamycin treatment works at least for a subgroup of CF-patients. The side-effects of gentamycin are being debated, and the authors point out correctly that other drugs (e.g., PTC124) may be more suitable, so gentamycin may not be the final answer. The study confirms that gentamycin is not generally effective for all stop mutations, but only for a sub-group. On the other hand, the study presents an in vitro method that seems to be able to predict the success of a clinical trial.

A drawback of the study is the small size of the groups. This results in a weak significance for the effects in the Y122X group. While this is maybe unavoidable for a relatively rare mutation, it poses some problems. There is also the question that the Y122X group does not react homogeneously – some patients react clearly to gentamycin, whereas others don’t react at all. Does this imply that other factors besides the genotype are important for the success of the treatment?

The practical consequences of the study seem to be limited, in that gentamycin is not effective for all class I mutations (about 10% of the CF-patients worldwide), but only for a small subgroup (a relatively rare mutation), and maybe not even for all patients in this subgroup. So the number of patients that might benefit from gentamycin treatment may be very small.

While this may detract from the impact of the paper, the positive side is that the study at least provides a basis for progress in the pharmacological treatment of CF.

None

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its
What next?: Accept for publication in BMC Medicine after discretionary revisions

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests