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LETTER TO THE EDITOR

On the demanding necessity of properly evaluating renal graft function in clinical trials

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Burke *et al.* [1] have recently questioned the necessity of using a direct method of GFR measurement in kidney transplant trials suggesting that the predictive performance of the Cockcroft–Gault, Nankivell or the MDRD study equations was sufficient to appropriately detect a treatment difference in renal graft function.

This statement is at odds with many, if not all, of the recent recommendations that have pinpointed the various limitations of predicting GFR from serum creatinine value in kidney transplantation [2–4].

Burke *et al.* based their conclusion on the finding that the three equations give a similar difference in mean GFR between the two treatment groups of a sirolimus trial. Importantly, as no reference method of GFR measurement was used as a comparator, one cannot rule out the possibility that all the three equations give a similar but erroneous conclusion.

In order to directly address the potential dangers of estimating rather than measuring GFR in transplantation research protocols, we performed several simulations from a previously described cohort of 500 inulin clearances [5]. This cohort was split into two groups of $n = 250$ each, either according to the date of transplantation (sorted by chronological order, simulation #1) or according to the recipient's age (sorted by increasing age, simulation #2).

For simulation #1, the mean true GFR significantly differed between the two groups, and so did the mean GFR estimated by the MDRD study equation. However, differences were no longer significant when the Cockcroft–Gault or the Nankivell equations estimated the GFR. In other words, had these equations been used in a hypothetical trial reproducing these conditions, the real beneficial effect of the tested therapy might have been missed (Table 1). Conversely, in simulation #2, the mean true GFR was not different between the two groups, and neither was the mean estimate given by the Nankivell and the MDRD study equations. But here, the Cockcroft–Gault equation did give a significant difference between the two groups (Table 2).

On the same lines, a recent trial has been reported on the effect of a new CTLA4 fusion protein (belatacept) in renal transplantation [6]. Among the secondary endpoints, the effect on the GFR at 1-year post-transplant has been analyzed. Interestingly, while belatacept was found to have a beneficial effect when GFR was measured by a reference method (iohexol clearance of 66.3 and 53.5 ml/min/1.73 m^2 for the belatacept-based treatment group and the cyclosporine A-based treatment group, respectively), no significant difference was reported

Table 1. Comparison of mean GFR between two fictitious groups of transplant patients (simulation #1).

	Group A mean ± standard deviation (ml/min/1.73 m^2)	Group B mean ± standard deviation (ml/min/1.73 m^2)	*P*-value (*t*-test)
Inulin clearance	45 ± 16	53 ± 22	<0.0001
MDRD	47 ± 17	52 ± 22	0.014
Cockcroft–Gault	52 ± 17	54 ± 20	0.125
Nankivell	56 ± 16	58 ± 20	0.067

An historic cohort of 500 inulin clearances (true GFR) is split into two groups of 250 clearances each, according to the date of transplantation.
The difference in mean GFR (either the true GFR or the GFR estimated by different equations) between the two groups is evaluated using a Student's *t*-test.

Table 2. Comparison of mean GFR between two fictitious groups of transplant patients (simulation #2).

	Group A mean ± standard deviation (ml/min/1.73 m^2)	Group B mean ± standard deviation (ml/min/1.73 m^2)	*P*-value (*t*-test)
Inulin clearance	51 ± 19	47 ± 21	0.119
MDRD	50 ± 19	49 ± 21	0.668
Cockcroft–Gault	57 ± 19	48 ± 18	<0.0001
Nankivell	57 ± 16	57 ± 19	0.978

An historic cohort of 500 inulin clearances (true GFR) is split into two groups of 250 clearances each, according to the recipient's age.
The difference in mean GFR (either the true GFR or the GFR estimated by different equations) between the two groups is evaluated using a Student's *t*-test.

between the two groups when GFR was estimated by the MDRD equation (72.4 and 68.0 ml/min/1.73 m^2 for belatacept and cyclosoprine A group, respectively).

As stressed by Burke *et al.*, we do acknowledge that using a creatinine-based GFR equation is likely to limit the rate of missing GFR values. Still, this has to be balanced with the risk of measuring an endpoint with a non-optimal method. Moreover, appropriate methodology has been described to efficiently circumvent the problem of missing data in this context [7].

Finally, we have to keep in mind that some of key clinical trials in nontransplant CKD patients have successfully and convincingly incorporated reference methods of GFR measurement to evaluate primary endpoints [8–10].

Should not the transplant clinical trials measure up to the same standard of quality?

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