Medical Therapies to Reduce Delayed Graft Function and Improve Long-Term Graft Survival

Are We Making Progress?

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Delayed graft function (DGF) is defined by the United Network for Organ Sharing (UNOS) as the need for at least one dialysis treatment in the first week after kidney transplantation. Because dialysis may be performed for indications unrelated to graft dysfunction (*e.g.*, hyperkalemia or fluid overload), the UNOS definition of DGF is widely acknowledged to be imperfect. However, it is used for uniformity in data reporting, and in most DGF studies. With rates reported to range between 25% and 30%, DGF has been associated in outcomes studies with increased hospital stay, increased rejection, and shorter graft survival (1). The mechanism underlying DGF, in its truest sense, is thought to primarily be related to ischemia-reperfusion injury, with ischemia from a variety of donor characteristics superimposed upon immune and inflammatory responses peri-transplant and postreperfusion, leading to acute tubular necrosis.

Given its important clinical implications, DGF has long been an active area of basic and clinical investigation. In this issue of *CJASN*, Huang *et al.* report the use of a novel therapeutic intervention for DGF (2), adding to the many treatments that have been tested in clinical trials and either published previously or currently remain under investigation. As shown in Table 1, most published studies have been disappointing in that they have shown minimal or no difference in DGF rates with intervention, or no eventual effect on allograft function or survival (3–7). For example, an initial study on donor therapy with dopamine showed promise, with reduced recipient dialysis needs; however, a larger-scale study ultimately failed to show improvement in 5-year graft survival (4). Similarly, hypothermic machine perfusion of deceased donor kidneys, as compared with cold storage, has been shown to decrease rates of DGF; however, the effect on long-term allograft survival is unknown (7). Thus far, the only intervention shown, albeit in a small, open-label, single-center study, to reduce DGF that has gained traction in clinical practice is the use of intraoperative rabbit anti-thymocyte globulin administered before reperfusion; however, no larger-scale, blinded trials have been undertaken to validate this (8). Delayed use or minimization of calcineurin inhibitors has been assumed to lower DGF rates or shorten DGF duration, but evidence supporting this strategy and/or how this translates into longer-term outcomes is lacking.

The study reported herein by Huang *et al.* represents *post hoc* follow-up of the original randomized trial of 70 deceased donor kidney recipients at risk for DGF, randomized 1:1 to receive C1 esterase inhibitor or placebo intraoperatively and again at 24 hours (9). Although the intervention did not lead to decreased rates of DGF, there was a trend toward shorter duration of this complication. The authors have now examined outcomes after 3.5 years in the form of graft failure and death, as well as eGFR slopes using linear mixed-effects model with random slopes and intercepts. While overall graft failure was not significantly different between the two groups, death-censored graft loss occurred in seven participants in the placebo group compared with one patient in the treatment group (P=0.03), whereas there were no deaths in the placebo group versus three in the treatment group (P=0.09). Functionally, the GFR slope rate declined in the placebo group (−4 ml/min per 1.73 m^2 per year; 95% confidence interval, −8 to −0.1) but remained stable in the treatment group (0.5 ml/min per 1.73 m^2 per year; 95% confidence interval, −4 to 5). Huang *et al.* conclude that treatment of patients at risk for ischemia-reperfusion injury with C1 esterase inhibitor was associated with a lower cumulative incidence of death-censored graft failure and a higher GFR at 3.5 years (P=0.05).

Although the findings of this well matched, randomized, double-blind, placebo-controlled trial are interesting, the sample size is small and the low percentage of black participants restricts the study generalizability, as pointed out by the investigators. Furthermore, the absence of other key information additionally constrains how one should interpret these findings. For example, not providing cause of graft failure limits the ability to determine whether the observed effect of C1 esterase inhibitor on death-censored graft survival was in any way related to an effect on DGF or ischemia-reperfusion injury. It is also unclear how graft loss and death was accounted for in the GFR slope analysis and how this might have

Table 1. Selected published and registered randomized, controlled DGF trials

Published Trials				
Intervention	Target	Cohort Size	Results	Reference
Eculizumab	Complement C5a	*n*=27	No difference in DGF rate, GFR at 6 mo	3
Dopamine (donor treatment)	Multiple	*n*=487	No graft survival advantage on intention to treat analysis	4
Epoetin-α	Multiple sites	*n*=72	No difference in DGF, SGF, and IGF rate and GFR at 1 mo	5
rPSGL-Ig (YSPSL)	Leukocyte adhesion blockade	*n*=59	No difference in DGF rate	6
Hypothermic machine perfusion	Multiple sites	*n*=80	Reduce risk of DGF, mean eGFR higher at 28 d and 1 yr	7

Registered Trials (Clinicaltrials.gov accessed October 19, 2019)				
Intervention	Target	Stage/Estimated Enrollment	End Point(s)	Clinicaltrials.gov ID
Envarsus XR versus tacrolimus	Fluctuations in tacrolimus levels	Recruiting *n*=100	Duration of DGF	NCT03864926
QPI-1002	siRNA targeting p53 gene	Completed *n*=594	Number of dialysis sessions at 30 d post-transplant in older recipients of DBD kidneys	NCT02610296
BB3	Hepatocyte growth factor	Recruiting *n*=242	Duration of DGF/number of dialysis sessions at 30 d post-transplant	NCT02474667
QPI-1002	siRNA targeting p53 gene	Completed *n*=374	Safety and incidence of delayed graft function	NCT00802347
OPN-305	TLR-2	Completed *n*=252	Dialysis initiation and failure of creatinine to decrease by 10% daily on three successive days during first 7 d post-transplant	NCT01794663
Renaparin in machine perfusion solution	Multiple	Recruiting *n*=18	Safety/adverse events in 30 d	NCT03773211
Mild hypothermia and machine perfusion	Multiple	Recruiting *n*=2800	Incidence of DGF	NCT02525510

DGF, delayed graft function; SGF, slow graft function; IGF, immediate graft function; ID, identifier; siRNA, small interfering RNA.

affected their findings. Finally, although the authors state that the placebo group's graft failure rate is similar to published rates for recipients of kidneys with a kidney donor profile index (KDPI)>85%, it is important to note that only 30% of placebo group patients received such kidneys, in which case the expected graft failure rate should be lower (2).

The rationale for evaluating C1 esterase inhibition to prevent DGF makes sense, given that *(1)* the predominant underlying mechanism is thought to be from ischemia-reperfusion injury, *(2)* the classic and mannose-binding lectin pathway have been implicated in ischemia-reperfusion injury, and *(3)* animal data have shown that targeting these two pathways prevents and/or attenuates ischemia-reperfusion injury and immune activation (2). Because prior research has not yielded much in the way of interventions to reduce DGF and improve allograft outcomes, Huang *et al.*'s preliminary investigation into C1 esterase is both commendable and worth considering to expand into a larger, more robust, multicenter trial. That said, it is important to point out that although the three treatment group deaths observed in their study all occurred more than 1.5 years after C1 esterase inhibitor treatment and may be unrelated to its administration, this adverse outcome nevertheless constitutes a safety signal that warrants close monitoring if this therapy were to be investigated further. A final consideration is whether enthusiasm for C1 esterase inhibition in this setting should be tempered by the fact that recent multicenter, randomized, controlled trials evaluating eculizumab in DGF failed to demonstrate a benefit to blockade of complement activation (*e.g.*, Schröppel *et al.* [3]). Although the answer to this question is unknowable at present, it is possible that blocking a more proximal site of action on the complement pathway and/or the inhibition of noncomplement pathways (*i.e.*, inhibition of activated factor XII, active kallikrein, factor XIa, and thrombin) by the C1 esterase inhibitor could result in a different effect, as some have proposed (10).

In summary, DGF remains a major clinical challenge for the transplant practitioner. In addition to efforts aimed at better defining DGF in the context of ischemia-reperfusion injury, and research focused on more clearly elucidating its biology, a growing number of treatment strategies and interventions are being investigated, at the level of donors, organ preservation, and therapies administered perioperatively to recipients (Table 1). The complement pathway,

a major component of the innate immune system, is being increasingly recognized as a potential mediator of ischemia-reperfusion injury. For this reason, the innovative approach undertaken by Huang *et al*. should be applauded, but more answers are clearly needed regarding the safety and efficacy of C1 esterase inhibition in preventing DGF. Finally, at a fundamental level, understanding how exactly DGF leads to increased rejection risk and worse long-term graft survival remains a critical unmet need in kidney transplantation. We look forward to the results of the several ongoing studies that are currently underway in this fertile area of investigation.

Disclosures

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See related article, "Three-Year Outcomes of a Randomized, Double-Blind, Placebo-Controlled Study Assessing Safety and Efficacy of C1 Esterase Inhibitor for Prevention of Delayed Graft Function in Deceased Donor Kidney Transplant Recipients," on pages 109–116.