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Predictors of graft function and survival in second kidney transplantation: A single center experience

Predictors of graft survival in second kidney transplantation

Fernando M Gonzalez

Abstract:

Kidney transplantation is the best option for kidney replacement therapy, even considering that most of the times the grafts do not survive as long as their recipients. Khalil *et al* analyze their second kidney graft survival and describe those significant predictors of early loss.

The editorial comments Khalil *et al* results and put in perspective that most of the times, long term graft survival could be inadvertently jeopardized if the immunosuppressive therapy is reduced or withdrawn for any reason, and that it could happen frequently if the transplant physician intend to innovate with the clinical care without proper evidence based data.

Key Words: Kidney transplantation; graft survival; acute rejection; IFTA; immunosuppression

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Core Tip: Most of the times, kidney graft and recipient survivals do not match because of earlier graft failure. Apart of surgical or urological complications, the reason frequently is the appearance of donor specific antibodies that mediate acute and chronic allograft damage because treating physicians intend to construct a tailor-made immunosuppressive therapy to each of their patients.

INTRODUCTION

Manuscript: Predictors of graft function and survival in second kidney transplantation: A single center experience.

Kidney transplantation is the best option for kidney replacement therapy, even considering that most of the times the grafts do not survive as long as their recipients. In those patients who experience the failure of the transplanted graft, it is still possible to perform a second, or even a third transplant, because these organs still perform better than dialysis.

From a process management perspective, the best option to prolong the survival of those patients suffering from end stage renal disease is to optimize dialysis quality while they are waiting for a transplant. Then, trying to prolong the survival of their first kidney graft. The question is how to accomplish this last issue in the real world.

In 1906, Vilfredo Pareto postulated that 80% of the consequences come from 20% of causes (1) and from this perspective, the main causes of transplant failures should be few. In the Khalil *et al* experience, published in this issue of the Journal, they state that the first graft failed mainly because of two drivers: Primary non-function, explained by a recipient high body mass index (P = 0.009), and first graft loss because of acute rejection (P = 0.025).They also found that the survival of the second graft was reduced if the first or the second one presented delayed graft function (P = 0.008, and p < 0.001, respectively) , and also if the first graft underwent an acute rejection in the first year after the first transplant (P = 0.053) (2). It is possible to think that Khalil describes two main determinants that explain their failures: rejection due to primary non-function, and immunological and inflammatory progressive damage to the graft. The first

determinant may be explained by organ donor maintenance quality before organ harvesting, cold and warm ischemia times lasting too long, and not enough expertise of the implanting surgeons, which are expected to decrease as the procurement and surgical teams get experience, as it is observed in countries with high rates of kidney transplants (3). Regarding the second determinant, it is more difficult to avoid having acute rejection episodes because there are several graft-recipient pair factors that intervene in their development , such as HLA mismatches, prior sensitization, immunosuppressive schemes, drug quality, and patient compliance, to mention a few.

Putting our focus on rejection, there are several experiences that analyze grafts biopsies from failing kidney transplants that intend to answer why those kidney grafts fail in the medium-to-long-term. Most of the time, it is found either graft rejection (9-64%) or non-specific chronic injury or, in other words, interstitial fibrosis and tubular atrophy (IFTA) (24-47%) (4).It is also found that the rejection types and IFTA vary in parallel with the recipients' age and time after transplantation. But characteristically, there are more T-cell mediated rejections (TCMR) before the first 5 years after transplantation, more antibody mediated rejections (ABMR) and IFTA after that period, and other causes of graft failure happen in young recipients (5).

By the way, what is IFTA? Is it synonymous with the chronic allograft nephropathy (CAN) term? At the end of last century, some experts thought that as grafts get older they accumulate specific and non-specific damage resulting in sclerosis, increase in the interstitium collagen content, and tubular atrophy. This hypothesis was endorsed in a prospective protocol biopsy cohort of both kidney and pancreas transplantation in type 1 diabetics (6). In fact, in this experience, Nankivell *et al* showed that rejections predominated soon after transplantation, and both chronic damage and arteriolar hyalinosis predominated later on. Regrettably, a secondary hypothesis resulting from this experience was that calcineurin inhibitors (CNI), mostly cyclosporine, could be the culprits, which stimulated the transplant community to the non-evidence based action to decrease or even withdraw the use of CNI. Some years later, we observed the appearance of donor specific antibodies (DSA), and subsequently, of ABMR and grafts

losses as consequences. The histological morphology of these grafts reminded of the old CAN and, at the same time, the newer term of IFTA, closing the circle of the main cause of the mismatch of kidney graft and transplanted recipient survivals, which is a chronic allograft rejection due to insufficient immunosuppression.

Nevertheless and sadly, this is not the whole story. Not providing enough immunosuppression could happen also because some doctors aspire to prescribe "patient tailored therapies" based on their own perceptions/experiences, and believing more on that than on evidence based medicine. There are several experiences, systematic reviews, and meta analyses that show us that decreasing, or even worse, withdrawing any of the chronic immunosuppressive agents such as CNI, antiproliferative, or steroids, is associated either to the appearance of DSA, ABMR, and IFTA. These pathogenic mechanisms would be the responsibles of the decrease in grafts survival and early graft loss (7)(8)(9)(10)(11)

Another explanatory variable could be frequent mycophenolate dose reduction, to even 50% below the standard and approved dose, occurring soon after transplantation, which is further associated with increase in IFTA (12) (13) Moreover, this unintended and naïve behavior, which tries to ameliorate drug related adverse events, could be accompanied with a decrease in CNI dose, resulting in less immunosuppression than prudence suggests (14)

From Khalil *et al* data, it is interesting to learn that for achieving a long kidney transplant survival it is advisable to be prepared in different frontlines. First, having a well-trained team in order to surpass surgical technical difficulties, such as primary non-function because of recipient's body mass index. And second, prescribing a well-balanced immunosuppressive therapy to maximize patients' adherence, minimize the probability of DSA, ABMR, IFTA, and of course, drug-related adverse effects appearance. Issues that may threaten the task of prolonging the survival of a first (or second) transplanted allograft with the objective of matching it with the survival of the recipient blessed by that transplant.

CONCLUSION

From Khalil *et al* data, it is interesting to learn that for achieving a long kidney transplant survival it is advisable to be prepared in different frontlines. First, having a well-trained team in order to surpass surgical technical difficulties, such as primary non-function because of recipient's body mass index. And second, prescribing a well-balanced immunosuppressive therapy to maximize patients' adherence, minimize the probability of DSA, ABMR, IFTA, and of course, drug-related adverse effects appearance. Issues that may threaten the task of prolonging the survival of a first (or second) transplanted allograft with the objective of matching it with the survival of the recipient blessed by that transplant.

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