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Effect of Delayed Graft Function in Hypersensitized Kidney Transplant Recipients

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ABSTRACT: There is increased evidence about the deleterious effect of delayed graft function (DGF) in both short- and long-term kidney graft outcome. Among the mechanisms involved in the production of DGF, immune factors play a role, especially in the level of hypersensitization. From the 1389 patients transplanted at our hospital until November 2004, it has been found that the presence of moderate and high levels of sensitization, as measured by panel-reactive antibodies, is a risk factor for suffering from DGF. Further, DGF was associated with poor graft survival, and the risk was even higher when DGF was combined with moderate/high panel-reactive antibodies. Recent data demonstrate the usefulness of intravenous immunoglobulins in the management of hypersensitized patients in terms of short-term outcome. It remains to be demonstrated whether this therapy is able to ameliorate the higher ischemic injury that kidneys undergo from these immunologically high-risk patients. *Human Immunology 66, 371–377 (2005).* © American Society for Histocompatibility and Immunogenetics, 2005. Published by Elsevier Inc.

KEYWORDS: delayed graft function; graft outcome; hypersensitization; intravenous immunoglobulins; ischemic injury

ABBREVIATIONS

AR	acute rejection
DGF	delayed graft function
HLA	human leukocyte antigen
HS	hypersensitized
IVIG	intravenous immunoglobulin
PRA	panel-reactive antibody
SGF	slow graft function
TNF-α	tumor necrosis factor alpha

Now that kidney transplantation has become the preferred choice for treating end-stage renal disease, and now that acute rejection (AR) and short-term graft outcome have been resolved, the challenge we now face is to improve the long-term graft outcome and the patient outcome [1]. These aims have been complicated by the ever-increasing number of patients on transplant waiting lists and the difficulties associated with the shortage of available organs [2]. Further, the criteria for selecting donors are expanding, with marginal kidneys now being transplanted, and an important percentage of patients undergo repeat renal transplantations [3]. These patients have been sensitized by previous human leukocyte antigen (HLA)-mismatched transplants and, probably, by blood transfusions and pregnancy [4]. Such patients are termed "hypersensitized" (HS) when exhibiting 50% or more panel-reactive antibodies (PRAs), although there is controversy about the exact PRA to define them, mostly because any titer of antibodies is associated with poorer graft survival [5].

Hypersensitized recipients with PRA >50% represent 9.2% of the waiting list at our hospital. These patients usually stay on the waiting lists of transplant centers for a long time because the crossmatch tests are positive—and if they are not, the requirements for HLA matching are so strict that is almost impossible to find a suitable donor. The use of marginal kidneys, together with the increased number of HS patients, largely contribute to the development of delayed graft function (DGF), which is one of the major risk factors for poor graft outcome and long-term patient outcome [6]. Important advances have been made by improving the perioperative management, but DGF is still a major impediment to the progression of kidney transplanta-

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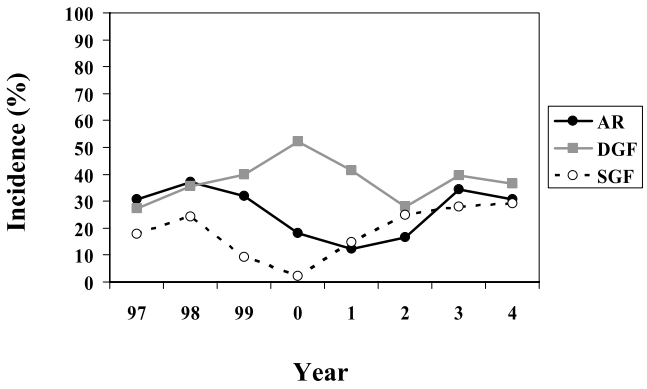

FIGURE 1 Incidence of acute rejection (AR), delayed graft function (DGF), and slow graft function (SGF) in the last 8 years at the University Hospital Marques Valdecilla. DGF was defined as need for dialysis in the first week after transplantation. SGF was defined as a slow recovery of graft function that permits avoidance of dialysis.

tion. With regard to hypersensitization, recent approaches have been published that allow successful transplantation of crossmatch–positive receptors, mainly on the basis of the use of intravenous immunoglobulins (IVIG) and plasmapheresis [7].

There are different definitions of DGF, although the most widely used is that of poor urine output and requirement for dialysis within the first week after renal transplantation [8]. This definition has the limitations of nephrologist readiness to perform the dialysis, delay in diagnosis by up to a week, and inclusion of different levels of graft dysfunction [9]. To overcome these limitations, we and others have proposed the creatinine reduction ratio on posttransplant day 2 as an earlier parameter of renal allograft function [9, 10]. We believe that this is a more predictive factor for kidney graft function during the first year than the performance of dialysis because this parameter detects a group of renal transplant recipients with poor graft survival, even though they do not need dialysis therapy [10]. The immediate graft function is in the opposite side, and it represents active diuresis and rapid decreases in serum creatinine. In addition, another concept between DGF and immediate graft function has been introduced: slow graft function (SGF). Slow graft function means slow recovery of graft function characterized by a moderate degree of diuresis and slow decrease in serum creatinine, which permit avoidance of dialysis treatment [6, 11]. At our hospital, the mean incidence of DGF and SGF during the last 8 years was 37.49% and 15.51%, respectively (Figure 1). We observed a relationship between DGF and AR in the last 5 years, with a clear decrease in their incidence until 2002. New immunosuppressive therapies have probably allowed better management of rejection. However, the last 2 years have seen an increase the frequency of AR episodes, perhaps because of the calcineurin inhibitor–sparing protocols [12] and because of the increased use of expanded criteria (to address the donor shortage) in the last few years at our center [6].

A number of risk factors for DGF and SGF have been described: donor tissue quality, brain death, perioperative management, recipient variables, and immune factors [6, 13]. The aim of the present report was to focus on the immune risk factors for developing any type of immediate graft dysfunction and how the use of IVIG is rapidly changing this field.

It is well accepted that HS patients have a higher frequency of DGF, probably because preformed HLA antibodies are not detected in the crossmatch and induce a silent AR that is manifested as DGF [14]. Figure 2 illustrates the incidence of AR and immediate graft

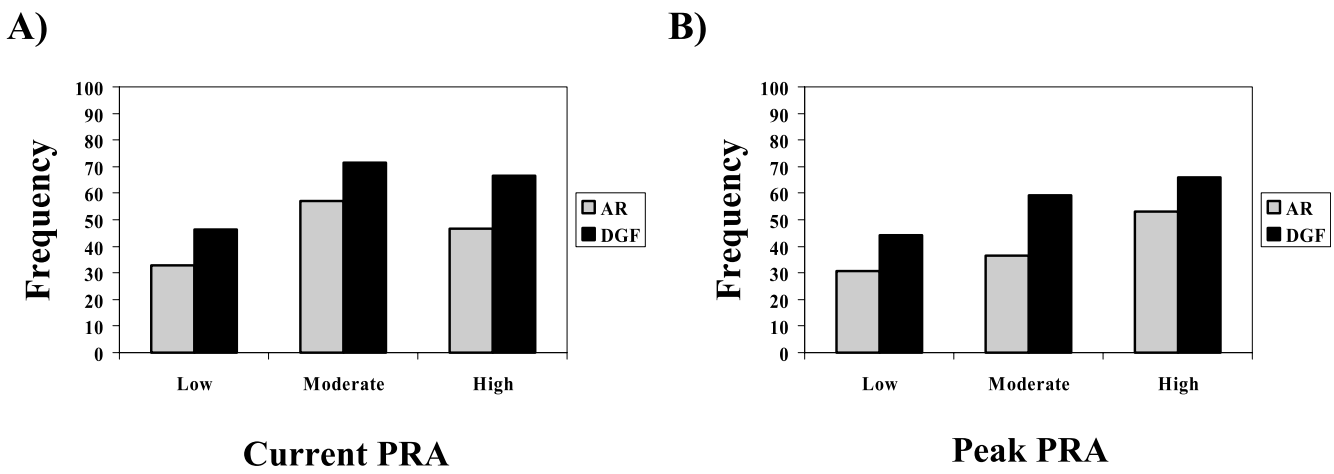

FIGURE 2 Frequency of acute rejection (AR) and delayed graft function (DGF) according to the current (A) and peak (B) panel-reactive antibody (PRA). Low level of sensitization was considered for PRA <25%, moderate for PRA 26%–50%, and high for PRA >51%. DGF-grouped patients experienced both delayed and slow graft function.