EDITORIAL

Immune biomarkers: do they impact long-term graft survival?

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The modern transplantation began to develop in the early 1950s, when Medawar et al[1] described actively acquired tolerance of foreign cells in rats. It heralded the beginnings of transplant immunology. A year later, in 1954, the first successful transplantation was performed in twin brothers. Since then, our understanding of the complex immunobiology of the immune system has considerably improved. Moreover, there has been a significant development in our knowledge on the molecular interactions responsible for immune response to grafts. Owing to the new immunosuppressive regimens, incidence of acute rejection episodes has decreased over the last decade. However, despite so many years of research, the major question remains as to how to make grafts live longer and retain sufficient function, as there has not been a similar improvement in long-term allograft survival. It may be due to the fact that a higher proportion of patients after episodes of acute rejection fail to recover baseline graft function. Moreover, high risk for cellular rejection is usually associated with high risk for antibody-mediated rejection, and a more common use of induction therapy may prevent acute cellular rejection in predisposed recipients, although at a potential cost of developing early interstitial fibrosis/tubular atrophy that is antibody-mediated and thus not easy to diagnose or treat. Also, potent induction agents might prevent acute rejections that are well and efficiently treated, and finally, lower incidence of acute rejection episodes is outweighed by over-immunosuppression with its side effects such as nephrotoxicity of calcineurin inhibitors.[2]

Graft biopsy is not an ideal technique: it is invasive and cannot be repeated as frequently as desired to closely monitor graft function. Thus, several studies were undertaken to look for other approaches to noninvasive monitoring of the immune response to the graft. In an ideal setting, the immune assay would detect rejection as early as possible, it would be both predictive and prognostic, and it would allow the accurate monitoring of the immune response. Thus, this assay might enable immunosuppressive therapy to be adjusted to minimize the adverse effects while maximizing the graft function. It could be a biomarker or biomarkers, easily measured, cost-effective, widely available, and with a comparable value to that obtained from biopsy. No such biomarker or biomarkers are currently available. Donor-specific antibodies to donor major histocompatibility complex are commonly used for immune monitoring in kidney transplantation. They can be measured before and after transplantation, and their presence indicates antibody-mediated rejection and may also be useful in chronic rejection.[3]

It should be stressed that patients with end-stage renal disease, who are broadly sensitized to human leukocyte antigens (HLAs) via previously administered blood products, pregnancy, or prior transplantation, often possess antibodies directed against deceased-donor and potential living-donor kidneys. In detail, HLA class-I antibody is related to pregnancy and blood transfusion, whereas HLA class-II antibody is related to a poor allograft survival rate. Both class-I and class-II antibodies are related to allograft loss.[4,5] In addition, nondonor HLA antibodies are also reportedly related to graft outcome.[6]

The available assays have not been extensively studied in relation to overall alloreactivity. Moreover, they define sensitization against the broad spectrum of potential donors, while the crossmatch identifies antibodies against a specific donor. Importantly, the overall clinical relevance of the antibodies detected may vary and, in some cases, is uncertain. It should be also stressed that there are no global standards for desensitization protocols, such as plasmapheresis or rituximab, with regard to sensitization status.[7] There are also several other limitations to the assessment of alloreactivity. Immunoglobulin (Ig) G antibodies

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detected by sensitization or crossmatch assays are generally considered to reflect true sensitization against HLA, while IgM antibodies are not considered typical of a true anti-HLA response. In general, antibodies detected against T cells have been considered to represent true anti-HLA sensitization against class-I antigens, whereas antibodies detected against B cells have been considered to represent HLA class-II antibodies. The latter are of lower clinical significance. However, B cells also express HLA class-I antibody, even at higher levels than T cells. Thus, T–cell-negative/B–cell-positive reactions may be secondary to either class-I or class-II antibodies. On the other hand, as class-I antigen is expressed on both T and B cells, T–cell-positive/B–cell-negative reactions are most likely due to a non-HLA antibody.

Antibodies are considered to be cytotoxic when they fix complement and produce a positive assay. However, using assays not based on complement fixation, such as flow cytometric assays or single-antigen bead assays (eg, Luminex assays) other types of antibodies could be detected. They may be not cytotoxic and their clinical significance is unclear. A positive-flow crossmatch is associated with an increased risk of rejection and decreased graft survival; in the case of the positive assay not based on complement fixation, the predictive value of this assay depends on the presence of donor-specific antibodies (DSAs) and their ability to fix complement.[8,9] Of note, most assays detect the presence of antibody but not the precise HLA specificity. In addition, assays for identification of antibodies targeted at specific HLA, such as Luminex, require extra time to be performed. This can be done only when time constraint is not a problem, such as in transplantation from a living donor.

According to Ciszek et al,[10] there are scarce data on the effects of anti-HLA antibodies on the long-term graft survival and its function. They studied 457 kidney recipients during a regular outpatient visit. They evaluated anti-HLA (classes I and II) and histocompatibility class I chain-related antigen A (MICA), using Luminex assays. It should be stressed that the follow-up period was 7 years. They found that anti-HLA but not anti-MICA antibodies in randomly obtained blood samples were the significant predictors of late kidney graft failure. The authors elegantly described the limitations of the study, which was single-center, cross-sectional, retrospective, and assessed only anti-HLA antibodies but not DSAs. They also acknowledged that some potentially relevant clinical data were not available but would be worth to know, such as a history of rejection episodes (acute or chronic), biopsy-proven reasons for graft loss, number and type of blood transfusions, and number of previous pregnancies. Owing to this shortcoming, the design of their future prospective studies includes more clinical data to prove or disprove that anti-HLA antibodies may serve as the biomarkers of the long-term kidney outcome after kidney transplantation. In conclusion, they suggested that the assessment of anti-HLA antibodies in kidney transplant recipients may identify a subgroup of patients requiring individualized posttransplant treatment, and such an approach could be also cost-effective. This statement is in line with the study of Ishida et al,[11] who reported that addition of rituximab lowered the incidence of biopsy-proven graft rejection and the presence of DSAs. This approach has a strong impact on graft rejection both in the short and long term as well as on graft survival. They also reported higher appearance of the HLA class-II subtype among de novo anti-HLA antibodies. Their study was based on the previous data showing reduction of chronic antibody-mediated rejection by targeting B-cell immunity through methods such as a splenectomy and rituximab.[12] In living related recipients, patients with posttransplant HLA class-I and class-II antibodies either alone or in combination showed significantly lower 4-year graft survival.[13] In addition, HLA class-II antibodies were more frequent in patients with graft failure, even in the absence of class-I antibodies in this group.

As biopsy is an invasive procedure, the search for biomarkers continues. The study of Ciszek et al[10] became another stone to pave the way to progress in this field. Due to recent advances in immune monitoring as measurement of expressed genes (genomics) or proteins (proteomics), the management of kidney transplant recipients may change completely. Although currently several noninvasive assays are not used routinely in clinical practice and have to be validated, they may become helpful in the future both for diagnostic purposes and for monitoring the response to antirejection therapy. They may also improve immunosuppresion management in our patients. These assays could be used also to evaluate new novel immunosuppressive drugs and regimens. The US Food and Drug Administration approved the ImmuKnow assay to estimate the net state of the immune system in immunocompromised patients. It is based on the ability of CD4 cells to respond to mitogenic stimulation by phytohemagglutinin-L in vitro by quantifying the amount of adenosine triphosphate produced and released from these cells following stimulation. However, we still have no data on the prognostic and prospective value of this mechanism in transplant recipients. The study of Ciszek et al[10] will certainly fill the gap in knowledge on the impact of immune biomarkers on long-term kidney graft survival. Whether these markers will replace kidney biopsy, only the time will show.

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