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What is the Best Alternative for Highly Sensitized Patients Awaiting Kidney Transplantation?

Brad C. Astor[1]

[1]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

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See Clinical Research on Page 2629

Individuals on waiting lists for kidney transplantation in the US and Europe who are sensitized to human leukocyte antigens (HLA) due to pregnancy, blood transfusions, or prior transplantation, have a substantially longer waiting time for a compatible deceased donor organ compared to their counterparts. For those transplant candidates with an identified but incompatible living donor, alternatives to waiting for a compatible deceased donor are receiving a compatible organ through a paired living donor programs or desensitization followed by transplantation.

A prior analysis of data from the UK found no survival benefit of living-donor HLA-incompatible transplantation compared to matched controls remaining on the waiting list.[1] Conversely, an analysis of data from 22 centers in the US found a significant survival advantage for those undergoing HLA-incompatible transplantation from a living donor following desensitization compared to controls remaining on the waiting list or receiving a compatible transplant from a deceased donor.[2]

The answer to the question of which approach is best on average, in terms of mortality, depends on numerous pieces of information, including the probability and waiting time for a compatible deceased donor, the probability and waiting time for a compatible live donor through a paired donation program, the expected survival on dialysis during this waiting time, and expected outcomes from a compatible live donor or desensitization and transplant from an incompatible donor. As the prevalence of comorbidities in the population, dialysis care practices, and resultant expected survival on dialysis may differ substantially across countries, the question of which approach is best may also differ. Allocation practices for sensitized patients also differ substantially, affecting waiting times. Thus, population-specific analyses are needed to guide practices.

As no data from randomized trials are currently available, and none are expected in the near future, analyses of observational data will need to suffice to address this question. Utilizing observational data to compare different treatment approaches is subject to significant potential bias. While some sources of potential bias are nearly impossible to circumvent, others can be avoided, or at least substantially reduced, with appropriate study designs and analytic methods.

Noble, et al, provide data from all (n=326) highly sensitized patients listed at a single center in France.[3] Of these, 36 were included in the desensitization protocol, 149 received a transplant without desensitization, and 141 did not receive a transplant during the follow-up period (median follow-up of 7 years). Notably, 6 of the 36 patients entered into the desensitization protocol were not transplanted; 3 due to failure to remove antibodies and three due to complications. Intention-to-treat principles dictate that these patients be included as "treated" in the analyses. In contrast to previous studies, this cohort of desensitized patients included 8 deceased donor recipients. The authors used a time-varying exposure survival analysis to compare mortality with and without desensitization. They found no significant difference in survival for those patients who were desensitized, those who received a compatible organ without desensitization, and those who remained on the waiting list.

In analyses of observational data in which some patients receive a treatment and others do not, and where the timing of treatment differs from patient to patient, there is substantial potential for immortal time bias.[4] This occurs

Correspondence: Brad C. Astor, University of Wisconsin School of Medicine and Public Health, 1685 Highland Avenue, 5149 Medical Foundation Centennial Building, Madison, WI 53705-2281, USA. E-mail: bcastor@medicine.wisc.edu

when follow-up time is attributed to an individual during a time in which the event of interest (e.g., mortality) cannot occur or would not be counted had it occurred. For example, in wait-listed patients eventually receiving a transplant, the follow-up time prior to transplant cannot be attributed to the transplant, as the transplant would not have occurred if the patient had died. During this time, the patient is "immortal." Incorrectly including this follow-up time as accrued in the "exposed" (i.e., transplanted) group adds immortal time and inappropriately lowers their calculated incidence of death. Noble, et al, appropriately used a time-varying exposure, in which follow-up time accrued prior to desensitization was attributed to "non-exposed" (i.e., waiting list), as those patients had not yet been exposed to desensitization during that time. Their exposure status changes to "exposed" (i.e., desensitized) at the time of the procedure. The authors also used a landmark analysis, in which patients are assigned to one or the other group as of a specific time point, in this case 36 months after registration, the time at which point most of the transplants that will eventually occur had already occurred. The two analyses provided similar results. The landmark analysis, however, does not utilize all of the available follow-up time, excludes those patients with events (i.e., death) prior to the landmark time, and results in misclassification of exposure status for those transplanted after the landmark time.

An alternative method which uses all of the follow-up time after the exposure of interest and also accounts for potentially differential timing of exposure is "exposure density sampling."[5] In this method, all of the available patients alive and not yet "exposed" at the time of each "exposure" (i.e., transplantation) are sampled to serve as controls for that specific transplantation. This method also matches for the time of exposure (or non-exposure) which may reduce the impact of differences over time. If the sample size allows, a subset of non-exposed patients can be selected based on specific matching criteria to result in more comparable groups.

The study by Noble, et al, provides evidence that a desensitization protocol for HLA-incompatible kidney transplants can result in similar survival as remaining on the list awaiting a compatible donor organ in their population. As discussed above, similar analyses, utilizing appropriate methods to preclude immortal time bias, are needed for other populations. In addition, the question of what approach is best will also need careful consideration of quality of life and costs.

DISCLOSURE

The author declared no competing interests.

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